Computed Tomographic Pulmonary Angiography for Diagnosis of Invasive Mold Diseases in Patients With Hematological Malignancies

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(See the Editorial Commentary by Herbrecht and Roedlich, on pages 617–20.)

Background. Invasive mold diseases (IMDs) of the lung remain a challenge for immunocompromised patients. Although timely diagnosis and treatment are crucial for the outcome of the infection, the poor sensitivity of microbiological techniques and the limited specificity of chest high-resolution computed tomography (HRCT) often delay definitive diagnosis of these infections.

Methods. To explore the diagnostic utility of computed tomographic pulmonary angiography (CTPA) for detecting angioinvasive patterns of pulmonary infection, we performed a single-center, prospective, nonrandomized trial involving 36 patients with hematological malignancies who had clinical suspicion of IMD, as defined by European Organization for Research and Treatment of Cancer/Mycosis Study Group diagnostic criteria.

Results. We found that 5 of 5 patients with proven IMD had CTPA-positive findings consistent with interruption of the arterial vessels (concordance, 100%). CTPA findings were positive in 5 of 7 patients with probable IMD (findings for 2 were considered false negative because lesions were too small or not evaluable). In 15 of 24 patients with a final diagnosis of possible IMD, CTPA findings were negative for 14 patients and were positive for 1 patient, who had septic emboli associated with Staphylococcus aureus bacteremia. CTPA findings were positive in the remaining 9 patients with a final diagnosis of possible IMD at the end of the study.

Conclusions. We conclude that CTPA appears to be a promising tool to exclude the diagnosis of IMD in high-risk patients without specific findings on HRCT scans, and it is most useful in the presence of well-circumscribed lesions in which there is suspicion for IMD.

Invasive fungal infections, particularly infections caused by Aspergillus species, remain an important cause of morbidity and mortality in neutropenic and immunocompromised patients. Although reliable and timely diagnosis improves patient outcome, invasive tests such as bronchoscopy and lung biopsy are often not feasible in severely thrombocytopenic and neutropenic patients. Hence, non–culture-based microbiological techniques, such as serum galactomannan (GM) testing, play an increasingly important role in the diagnosis of invasive aspergillosis. However, the GM test has poorer sensitivity in nonneutropenic patients [1] and in patients receiving mold-active prophylaxis [2]. Moreover, false-positive results can occur during the administration of piperacillin-tazobactam [3], which is used in many hematology units as the front-line anti-pseudomonal antibiotic for febrile neutropenia [4].

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Whereas standard chest radiography often demonstrates normal or nonspecific findings during early phases of infection in up to 50% of patients with aspergillosis [5, 6], high-resolution computed tomography (HRCT) can, at earlier stages of disease, detect pulmonary infiltrates suggestive of invasive mold infections and is frequently used to monitor the response to therapy [7–9]. The most typical HRCT findings are nodules or large segmental consolidations that are surrounded by a halo of ground-glass attenuation (ie, the “halo sign”) [10–12] and correspond to hemorrhagic infarcts due to vascular invasion by fungal hyphae that have caused thrombosis and ischemic necrosis surrounded by a rim of coagulation necrosis [13, 14]. Previous studies have found that, in patients with antibiotic-resistant neutropenic fever, the halo sign is highly suggestive of angioinvasive aspergillosis, with diagnostic probability rates approaching 80%–100% [15–18]. Furthermore, HRCT can demonstrate the halo sign earlier than serum GM testing can identify aspergillosis [19]. However, the halo sign is neither sensitive nor specific for invasive mold disease (IMD) and is occasionally present in patients with pulmonary candidiasis, cryptococcosis, cytomegalovirus, neoplasms (eg, Kaposi sarcoma, and pulmonary metastases from hypervascular tumors), or other diseases (eg, Wegener granulomatosis and organizing pneumonia) [20, 21]. Therefore, halo signs are not considered to be definitive evidence of invasive mold disease (IMD).

More recently, a small prospective study by Sonnet et al [22] suggested the possible diagnostic utility of CT pulmonary angiography (CTPA) with 16-multidetector CT to directly detect, at an early stage, the angioinvasive pattern of pulmonary aspergillosis or mucormycosis in immunosuppressed patients with fever of unknown origin. CTPA with multidetector CT has improved the detection of pulmonary embolism [23]; hence, this technique can be very useful to show the direct vessel occlusion at the level of a focal lesion due to IFD.

Because these observations suggest that CTPA could improve the diagnostic specificity of chest imaging for mold pneumonia, we performed CTPA in 36 patients with hematological malignancies who had a high clinical suspicion for IMD on the basis of revised European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) criteria [24]. The purpose of this study was to examine the correlation between imaging findings and clinical/microbiological findings, as well as the possible utility of CTPA for improving the identification of patients with mold disease classified as “possible disease” on the basis of current EORTC/MSG criteria.

**METHODS**

**Patient Population**

The diagnostic utility of CTPA was explored in a single-center, prospective, nonrandomized trial at the Institute of Hematology “Lorenzo e Ariosto Seràgnoli,” Sant’Orsola-Malpighi Hospital, University of Bologna (Bologna, Italy). The study design was approved by the institutional research committees in accordance with principles outlined in the Declaration of Helsinki. We identified 36 patients with hematological malignancies between March 2008 and October 2010 who were at high risk for developing IFD. The most common underlying malignancies were acute myeloid leukemia and acute lymphoblastic leukemia, followed by myelodysplastic syndrome, lymphoma, chronic myeloproliferative disorder, and chronic lymphocytic leukemia (Table 1). A majority of patients (22 [61%] of 36) were not in remission at the time they were entered into the study. Most patients (23 [64%] of 36) were receiving chemotherapy, whereas 12 (33%) of 36 underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT). One patient was not receiving chemotherapy from the time of the study (Table 1).

In the study cohort, 23 (64%) of 36 patients had underlying malignancies (ie, acute myeloid leukemia or myelodysplastic syndrome) or received treatment associated with high risk of IMD (ie, allo-HSCT). Systemic antifungal prophylaxis was administered in 24 (67%) of 36 patients, including fluconazole (in 13 [36%]), itraconazole (in 5 [14%]), posaconazole (in 5 [14%]), and liposomal amphotericin B (in 1 [3%]) (Table 1).

**Chest Computed Tomography**

We enrolled 36 patients with clinical suspicion of IMD and HRCT findings of a pulmonary dense nodule or consolidation with a diameter ≥10 mm, with or without halo sign, without cavitation and/or the air-crescent sign. All patients were examined with a 16-multidetector CT scanner (Lightspeed; GE). After a basal scan for HRCT analysis (section thickness, 1.25 mm; reconstruction interval, 1 mm), CTPA was performed after intravenous administration of 70–80 mL of nonionic contrast media at a flow rate of 3–3.5 mL/sec, with a starting delay for pulmonary angiography of 12–15 seconds, using SmartPrep software (GE). Contrast administration was followed by a 30–40-mL saline flush at the same flow rate. Scanning was performed using a section thickness of 1.25 mm and a reconstruction interval of 1 mm. The CT images were transferred to a dedicated workstation (Advantage 4.3; GE), and 2-dimensional reconstructions were performed using multiplanar reformatting programs.

All images were evaluated by 2 expert radiologists blinded to the patients’ clinical courses and diagnoses. If disagreements occurred, the blinded radiologists discussed the findings and reached a consensus interpretation. HRCT images were analyzed for the presence of a dense nodule or consolidation (with data on number, size, and morphology recorded), with or without a halo sign. The CTPA axial images and the 2-dimensional maximum intensity projection–reconstructed images in coronal, sagittal, and oblique planes were analyzed for the presence of
vascular occlusion, which was defined, in accordance with Sonnet et al [22], as an interruption of a vessel at the border of a focal lesion, without depiction of the vessel inside the lesion or peripheral to the lesion. If a certain feature was present at least once in a patient, the patient was considered positive for this feature. CTPA findings consistent with true-positive, true-negative, false-positive, and false-negative cases are presented in Figure 1.

Diagnostic Assessment

Patients were investigated for IMD if they were neutropenic (absolute neutrophil count, <500 cell/mm³; 89%) and/or severely immunocompromised, were febrile 72–96 hours after initiation of empirical antibiotic therapy, and had 2 consecutive serum samples that tested positive for GM. All 36 patients had pulmonary infiltrates on HRCT scan suggestive of IMD, as defined by the EORTC/MSG consensus group criteria [24]. Proven IMD diagnosis required the identification of fungal elements, by culture or by histopathological, cytopathological, or direct microscopic examination of specimens obtained by sterile procedure from a normally sterile site, and the presence of a clinically or radiologically abnormal site consistent with infection. The criteria for probable fungal disease were presence of a host factor (ie, neutropenia, receipt of an allo-HSCT, prolonged use of corticosteroids, treatment with immunosuppressant drugs, or inherited severe immunodeficiency), radiographic features of IMD (ie, presence of dense, well-circumscribed lesions with or without a halo sign and/or air crescent sign and/or cavity on CT), and mycological evidence (ie, presence of mold in sputum, bronchoalveolar lavage [BAL] fluid, or bronchial brush or detection of GM antigen in plasma, serum, or BAL fluid). The category of possible IMD included patients with appropriate host factors and sufficient clinical evidence of infection but no mycological confirmation.

Serum GM testing (Platelia; Bio-Rad Laboratories) was performed twice weekly in almost all (34 [94%] of 36) patients with neutropenic fever, and results were considered positive if an optical density index of $0.5 was present. When possible (for 6 [17%] of 36 patients), the GM assay was also performed on BAL fluid (Table 1).

To ensure consistency in case assessment, a medical commission, including 2 hematologists and 2 radiologists, evaluated the concordance between the HRCT images (without angiographic study) and clinical/microbiological findings to determine whether a diagnosis that accorded with the EORTC/MSG criteria was justified. Afterward, these data were compared with the CTPA findings to determine their concordance.

Data Analysis

Characteristics of CTPA-positive patients were summarized and compared with characteristics of CTPA-negative patients by the

Table 1. Baseline Demographic Data and Treatment Characteristics of Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>CTPA-Negative Patients (n = 16)</th>
<th>CTPA-Positive Patients (n = 20)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (range)</td>
<td>52.5 (22–80)</td>
<td>52.5 (20–71)</td>
<td>.23</td>
</tr>
<tr>
<td>Male sex</td>
<td>9 (56)</td>
<td>10 (50)</td>
<td>.79</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML/MDS</td>
<td>5 (31)</td>
<td>11 (55)</td>
<td>.15</td>
</tr>
<tr>
<td>ALL</td>
<td>5 (31)</td>
<td>5 (25)</td>
<td>.85</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>5 (31)</td>
<td>1 (5)</td>
<td>.04</td>
</tr>
<tr>
<td>CMD</td>
<td>0</td>
<td>3 (15)</td>
<td>.11</td>
</tr>
<tr>
<td>CLL</td>
<td>1 (6)</td>
<td>0 (0)</td>
<td>.23</td>
</tr>
<tr>
<td>Disease phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete remission/chronic phase</td>
<td>6 (37)</td>
<td>8 (40)</td>
<td>.88</td>
</tr>
<tr>
<td>Initial diagnosis</td>
<td>1 (6)</td>
<td>6 (30)</td>
<td>.14</td>
</tr>
<tr>
<td>Relapse, resistance, or progression</td>
<td>9 (56)</td>
<td>6 (30)</td>
<td>.17</td>
</tr>
<tr>
<td>Malignancy treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction chemotherapy</td>
<td>1 (6)</td>
<td>5 (25)</td>
<td>.19</td>
</tr>
<tr>
<td>Consolidation chemotherapy</td>
<td>11 (69)</td>
<td>6 (30)</td>
<td>.001</td>
</tr>
<tr>
<td>Allogeneic HSCT</td>
<td>3 (19)</td>
<td>9 (45)</td>
<td>.16</td>
</tr>
<tr>
<td>No chemotherapy</td>
<td>1 (6)</td>
<td>0</td>
<td>.44</td>
</tr>
<tr>
<td>Antifungal prophylaxis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsystemic</td>
<td>6 (38)</td>
<td>1 (5)</td>
<td>.003</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>3 (19)</td>
<td>2 (10)</td>
<td>.63</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>4 (25)</td>
<td>9 (45)</td>
<td>.30</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>1 (6)</td>
<td>4 (40)</td>
<td>.14</td>
</tr>
<tr>
<td>L-AmB (1 mg/kg/d)</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>.08</td>
</tr>
<tr>
<td>None</td>
<td>2 (25)</td>
<td>3 (15)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Neutropenia at fever onsetb</td>
<td>13 (81)</td>
<td>19 (95)</td>
<td>.30</td>
</tr>
<tr>
<td>Serum galactomannan status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Index &gt;0.5</td>
<td>2 (25)</td>
<td>9 (45)</td>
<td>.07</td>
</tr>
<tr>
<td>Not assessed</td>
<td>2 (25)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>BAL galactomannan status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Index &gt;0.5</td>
<td>0</td>
<td>3 (15)</td>
<td>.24</td>
</tr>
<tr>
<td>Not assessed</td>
<td>15 (94)</td>
<td>15 (75)</td>
<td>.24</td>
</tr>
</tbody>
</table>

Data are no. (%) of patients, unless otherwise indicated. Percentages may not equal 100% because of rounding.

Abbreviations: ALL, acute lymphoblastic leukemia; AML/MDS, acute myeloid leukemia/myelodysplastic syndrome; BAL, bronchoalveolar lavage; CLL, chronic lymphocytic leukemia; CMD, chronic myeloproliferative disorder; CTPA, computed tomographic pulmonary angiography; HSCT, hematopoietic stem cell transplant; L-AmB, liposomal amphotericin B.

* Calculated using the Student t test, for continuous variables, or the Fisher exact test, for nominal variables.

b Defined as an absolute neutrophil count of <500 cells/mm³.
2-tailed Student t test, for continuous variables, or the Fisher exact test, for nominal variables. Differences were considered statistically significant at \(P < .05\). All analysis was performed with SPSS software, version 19 (SPSS).

RESULTS

On the basis of EORTC/MSG criteria, 5 (14%) of 36 patients had proven IMD, 7 (19%) of 36 had probable fungal disease, and 24 (67%) of 36 had possible fungal disease (Table 2). The 5 histologically proved cases included pulmonary aspergillosis (\(n = 4\)) and pulmonary mucormycosis (\(n = 1\)). The diagnosis of probable pulmonary fungal disease required pulmonary HRCT findings suggestive of IFD and a serum or BAL specimen positive for GM, whereas the 24 cases of possible IFD were defined as pulmonary HRCT findings suggestive of IFD (ie, dense, well-circumscribed lesions with or without a halo sign) [7, 25, 26] without any microbiological findings. A final diagnosis was established for each patient by the end of the study on the basis of microbiological data and/or clinical/radiological response, including the response to antibacterial and/or antifungal therapy (Tables 2 and 3).

CTPA revealed that all 5 cases of proven IMD at final diagnosis showed an interruption of the arterial vessels (concordance, 100%). In patients with probable IMD at final diagnosis, CTPA findings were positive in 5 (71%) of 7 cases. Two patients had negative CTPA findings. The first patient had small lesions (diameter, 10–12 mm) localized at the pulmonary apex, which was not amenable to clear visualization of vessels after CTPA imaging. Therefore, this case, the CTPA findings for which could not be read, was classified as false negative. In the second CTPA-negative case, the patient had underlying lymphoma at the site (confirmed by positron emission tomography or CT) with later development of additional nodules believed to be fungal infection that were detected 10 days later with follow-up HRCT. However, CTPA was not repeated because of the small size of the lesion, and the case was considered nonevaluable (ie, false negative).

With respect to patients with a halo sign at baseline, CTPA findings were positive in 12 (75%) of 16, compared with 4 (25%) of 16 with no halo sign (\(P < .001\)). Of the 4 patients with positive CTPA findings but no halo sign, 3 were later found to have other causes of pulmonary disease, including bacterial pneumonia in 1 patient, viral pneumonia in 1 patient, polymicrobial pneumonia in 1 patient, and lymphoma in 1 patient.

Table 2. Diagnostic Concordance Between European Organization for Research and Treatment of Cancer/Mycosis Study Group Criteria and Computed Tomographic Pulmonary Angiography

<table>
<thead>
<tr>
<th>EORTC/MSG-Based Diagnosis</th>
<th>CTPA-Positive Patients</th>
<th>CTPA-Negative Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven IMD ((n = 5))</td>
<td>Invasive aspergillosis ((n = 4))(^a), invasive mucormycosis ((n = 1))(^a)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Probable IMD ((n = 7))</td>
<td>Probable IMD ((n = 5))</td>
<td>Probable IMD ((n = 2))(^b)</td>
</tr>
<tr>
<td>Possible IMD ((n = 24))</td>
<td>Possible IMD ((n = 9)), bacterial pneumonia ((n = 1))(^c)</td>
<td>Bacterial pneumonia ((n = 11)),(^c) viral pneumonia ((n = 1)),(^c) polymicrobial pneumonia ((n = 1)),(^c) lymphoma ((n = 1))</td>
</tr>
</tbody>
</table>

Abbreviation: CTPA, Criteria and Computed Tomographic Pulmonary Angiography; EORTC/MSG, European Organization for Research and Treatment of Cancer/Mycosis Study Group; IMD, invasive mold disease.

\(^a\) Confirmed by autopsy or bronchoscopy.

\(^b\) Lesion was too small or not evaluable.

\(^c\) Pseudomonas aeruginosa (\(n = 1\)), Escherichia coli (\(n = 2\)), and resolution of lesions only with empirical antibiotic therapy (\(n = 8\)).

\(^d\) Influenza virus (H1N1) (\(n = 1\)).

\(^e\) Acinetobacter baumanii plus parainfluenza virus plus Epstein-Barr virus (\(n = 1\)).

\(^f\) Staphylococcus aureus (\(n = 1\)); septic emboli.
have proven IMD, with a fourth patient having only possible IMD (ie, only CT evidence of disease). Of the 2 patients who had halo signs on chest CT but negative CTPA findings, one was believed to have bacterial pneumonia (which improved rapidly during antibiotic therapy), and the other patient had a final diagnosis of possible IMD.

In 15 of the 24 possible IMD cases, the final diagnosis did not match the clinical and microbiological criteria for pulmonary fungal disease (Tables 2 and 3). Of these 15 patients, 3 had lung lesions that resolved without empirical antifungal therapy during episodes of *Escherichia coli* bacteremia (in 2) and *Pseudomonas aeruginosa* bacteremia (in 1). Lung lesions in another 8 patients resolved with empirical antibiotic therapy and without antifungal therapy. Finally, 3 patients had other causes for their lung lesions, including infection (H1N1 influenzae in 1 patient, and 1 patient with *Acinetobacter baumanii* plus parainfluenza and Epstein-Barr virus); or histological documentation of recurrence of their underlying malignancy in the lung (1 patient) (in 2 patients; 1 with H1N1 influenza virus and 1 with *Acinetobacter baumanii* plus parainfluenza virus and Epstein-Barr virus other) or histological documentation of recurrence of their underlying malignancy in the lung (in 1 patient). Notably, CTPA findings were positive in only 1 of these 15 patients; the patient had *Staphylococcus aureus* fasciitis with involvement of the left eye, as well as pneumonia arising from septic emboli. Although CT demonstrated multiple nodular lesions in this patient, only 1 nodule was determined to have interruption of arterial vessels. Therefore, the case was judged to be false positive.

In the other 9 of 24 patients with possible IMD, a final diagnosis of IMD was eventually confirmed. In all 9 cases, HRCT and CTPA findings were positive. The 9 patients with confirmed IMD received antifungal therapy for a median of 43 days (range, 14–146 days).

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**DISCUSSION**

Although early diagnosis of mold infection in severely immunocompromised patients is an essential component of the management strategy for these infections, differentiation of mold from other common pathogens that produce similar radiographic patterns can be challenging. The revised EORTC/MSG criteria extended the radiological diagnosis of possible IFD to include patients who have pulmonary dense lesions without a halo sign on HRCT scan [24], which may be seen in other pulmonary infections, including bacterial pneumonia, and also in certain malignancies, including lymphoma [27]. Thus, while the new definition includes a greater proportion of patients with less “classic” radiographic presentations of aspergillosis, it may also decrease the specificity of these radiographic findings for IMD.

As in previous studies [22], we wanted to test the capacity of pulmonary CTPA to discriminate between IMD and other conditions involving pulmonary infiltrates that, on the basis of CT imaging and the revised EORTC/MSG criteria, are similar to fungal infections. In our series, CTPA findings were positive in 5 of 5 proven cases, confirming the capabilities of CTPA to show the interruption of vessels at the border of the lesion. In 5 of 7 probable cases (ie, in patients with positive HRCT findings plus positive results of GM testing), an interruption of the vessels was evident by CTPA. However, 2 patients had negative CTPA findings that were eventually judged to be false negative. In 1 case, the pulmonary lesions were very small (diameter, 10–12 mm) and localized to the lung apex. These conditions (ie, small size and peripheral localization) probably confound assessment of vessel interruption because the vessel itself is too narrow in the periphery. Therefore, if small lesions are present on the HRCT scan, we suggest using CTPA as an adjunctive technique only if the lesions have a diameter of >12 mm and are not localized in peripheral lung parenchyma. In the second case, the patient had nodular lesions on HRCT scan and a positive GM test result. The corresponding CTPA showed clear vessels within the lesion, without interruption at the border, so this lesion was considered a manifestation of the underlying malignancy (ie, lymphoma), which was subsequently confirmed by positron emission tomography or CT. However, follow-up HRCT performed 10 days later showed a new lesion, which cavitated 3 weeks later and resolved after 13 days of systemic antifungal therapy, whereas the primary lesion ascribed to lymphoma remained unchanged. In this patient, CTPA was not repeated at the time of onset of the new lesion because of its small size. Thus, we are unable to state with certainty whether this case represents a true false negative.

On the basis of the EORTC/MSG criteria, 24 patients had possible IMD, but in 15 cases the final diagnosis did not match the clinical and microbiological criteria for IMD. In all but 1 of
the 15 cases, CTPA did not reveal interruption of the vessels at the border of the lesions. All 9 patients with possible IMD at final diagnosis were also CTPA positive. These data are encouraging because they suggest that a negative CTPA may have a high negative predictive value when combined with other means of clinical assessment for ruling out mold infection in the lung. The only patient with a documented false-positive CTPA result had pulmonary septic emboli. Radiographically, septic emboli are indistinguishable by IMD because the pathogenesis is similar; thus, the case was a false positive.

With regard to the appropriate time point for performing CTPA, we believe that CTPA should be performed in the early course of the disease at the time nodular lesions are initially identified by HRCT. In fact, the angioinvasion with vessel occlusion is an early pathogenic process, which probably is followed by the recanalization of the vessel [7]. Hence, a delayed scan would probably be less useful because at later stages occlusion of the vessel would be more difficult to visualize.

Our study had several limitations. First, the study involved a small number of patients. Second, although the patients were homogeneous with regard to the risk of IMD, the HRCT findings, and the CT acquisition parameters, a few had a definite diagnosis based on histological examination and most patients had a final diagnosis of possible IMD. Therefore, the pathological-radiological correlation is limited. However, the final diagnosis, which was established on the basis of clinical data, clinical or radiological course, and response to antifungal therapy, reflects the situation in clinical practice, where biopsy is rarely performed and culture results are absent or delayed. Finally, because the study was not randomized, it may have been influenced by unrecognized bias. Therefore, our results should be considered as only the initial step in evaluating the potential role and optimal timing of CTPA for invasive mold infections of the lung in high-risk patients.

Another limitation of performing angiography as an adjunctive test in patients with CT scans suggestive of IMD is that patients are exposed to additional CT and potentially nephrotoxic contrast dye. However, we believe these slightly increased risks are justified for most patients, because CT yields a more definitive diagnosis earlier during the infection, possibly allowing streamlining of empirical therapy and reducing the number of subsequent CT scans. The other advantage of pulmonary angiography is that this technique can be performed in most hospitals, and findings can be reported quickly. Other diagnostic tests, such as bronchoscopy and GM testing, are limited in many hospitals by either poor sensitivity or delayed reporting of results.

In conclusion, CTPA appears to be a promising approach for detecting vessel interruption at the border of a focal lesion and angioinvasion associated with IMD. CTPA seems to be a promising tool to exclude the diagnosis of IFD in high-risk patients with suspicious but nonspecific findings on HRCT scan, as patients with negative CTPA findings had significantly lower rates of proven or probable IFDs. In our experience, we have found CTPA most useful for high-risk patients with well-circumscribed lesions suggestive IFD, especially when other signs suggestive of invasive mold infection, such as a halo sign, are absent.

The most important limitations of this technique involve the size and localization of lesions: lesions that are too small (diameter, ≤ 12 mm) and localized in the periphery (ie, lung bottom or apex) are not exhaustively assessable. Therefore, we think this technique should be used only as an adjunctive study when HRCT shows lesions that have large diameters and are not localized in peripheral lung parenchyma. Larger prospective trials will be required to better define the benefits of CTPA for improving the sensitivity and specificity of IFD diagnosis in patients with hematological malignancies.

Notes

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Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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