Predictors of Pulmonary Zygomycosis versus Invasive Pulmonary Aspergillosis in Patients with Cancer

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Background. Pulmonary zygomycosis (PZ), an emerging mycosis among patients with cancer, has a clinical manifestation similar to that of invasive pulmonary aspergillosis (IPA). Most cases of PZ in such patients develop as breakthrough infections if treatment with antifungal agents effective against *Aspergillus* species is administered. However, clinical criteria to differentiate PZ from IPA are lacking.

Methods. We retrospectively reviewed the clinical characteristics and computed tomography (CT) findings for 16 patients with cancer and PZ and for 29 contemporaneous patients with cancer and IPA at the time of infection onset (2002–2004). Patients with mixed infections were excluded. Parameters predictive of PZ by univariate analysis were included in a logistic regression model.

Results. Almost all patients with PZ (15 of 16) and IPA (28 of 29) had underlying hematological malignancies and typical risk factors for invasive mold infections. In logistic regression analysis of clinical characteristics, concomitant sinusitis (odds ratio [OR], 25.7; 95% confidence interval [CI], 1.47–448.15; $P = .026$) and voriconazole prophylaxis (OR, 7.76; 95% CI, 1.32–45.53; $P = .023$) were significantly associated with PZ. The presence of multiple ($\geqslant 10$) nodules (OR, 19.8; 95% CI, 1.94–202.29; $P = .012$) and pleural effusion (OR, 5.07; 95% CI, 1.06–24.23; $P = .042$) at the time that the patient underwent the initial CT were both independent predictors of PZ in the logistic regression analysis of radiological parameters. No difference occurred in the frequency of other CT findings suggestive of pulmonary mold infections (e.g., masses, cavities, halo sign, or air-crescent sign) between the 2 patient groups.

Conclusions. PZ in immunocompromised patients with cancer could potentially be distinguished from IPA on the basis of clinical and radiological parameters; prospective validation is needed.

Invasive pulmonary aspergillosis (IPA) remains the major cause of death due to invasive fungal infections (IFIs) in heavily immunocompromised patients with leukemia and allogeneic bone marrow transplants (BMTs) [1]. However, an increasing incidence of zygomycosis in several cancer centers, in association with the increasing use of antifungal agents with anti-*Aspergillus* activity, such as voriconazole, has been recently reported [2, 3]. Because both zygomycosis and invasive aspergillosis afflict patients who have cancer and similar risk factors for IFIs, and because pneumonia is the predominant clinical presentation for both entities in such patients, distinguishing between these 2 mold infections is clinically difficult [2, 4]. Establishment of a definite diagnosis with biopsy in these patients is hampered by the presence of comorbidities, such as thrombocytopenia.

Thus, development of criteria to differentiate pulmonary zygomycosis (PZ) from IPA could have important therapeutic implications, because voriconazole, the preferred antifungal agent for the treatment of IPA [5], has no activity in zygomycosis [2]. In contrast, only amphotericin B–based therapy [6] and possibly posaconazole therapy [7] have been shown to have activity against Zygomycetes.

CT of the chest is a powerful tool for diagnosis of invasive mold infections (IMIs) in patients with hematological malignancies. However, in view of the fact that IPA is the most common IMI, the majority of contemporary studies have focused on the CT findings of IPA [8, 9]. On the other hand, the CT characteristics of PZ are less well studied [10]. Moreover, no study

has performed a head-to-head comparison of CT findings with clinical characteristics of PZ and IPA among the high-risk hematology population. To that end, we sought to identify radiographic and clinical parameters that at the onset of the infection may differentiate PZ from IPA.

MATERIALS AND METHODS

Patients and setting. For this retrospective study, we identified patients with cancer and PZ and contemporaneous patients with cancer and IPA who had been treated at our institution during the period of 1 September 2002 through 31 August 2004. Standardized criteria of the European Organisation for Research and Treatment of Cancer/Mycosis Study Group were applied for diagnosis of definite and probable PZ and IPA [11]. Patients with mixed pulmonary infections (i.e., fungal, bacterial, or viral infections) were excluded from the analysis.

The medical records for these patients were reviewed, and the 2 resulting groups were compared in terms of demographic characteristics, type and status of underlying malignancy, type of BMT (if applicable), and risk factors for IMIs present at diagnosis of infection, such as neutropenia (including duration), grade III–IV graft-versus-host disease (GVHD), malnutrition, receipt of adrenal corticosteroids (cumulative dose [prednisone equivalent] and duration) within the month before diagnosis, receipt of TNF inhibitors (e.g., infliximab) within 3 months before diagnosis, history of diabetes mellitus or hemodialysis, APACHE II score at the time of diagnosis of infection, and type and duration of antifungal prophylaxis. Information about the presenting symptoms of the infection and the clinical characteristics associated with PZ (e.g., sinus involvement) was also recorded for every patient. The in vitro susceptibility of Zygomycetes and *Aspergillus* isolates to antifungals was determined by the standard NCCLS M38-A broth microdilution method [12].

Case definitions. Malnutrition was defined as a serum albumin level of ≤3 g/dL, neutropenia was defined as a neutrophil count of ≤500 cells/mm³, and neutropenia during the month before diagnosis was defined as a neutrophil count of ≤500 cells/mm³ for >10 days. Antifungal prophylaxis was defined as the use of an antifungal agent with anti-*Aspergillus* activity (e.g., voriconazole, itraconazole, caspofungin, and amphotericin B) for >5 continuous days without any signs or symptoms of IMI. Significant corticosteroid use was defined as receipt of >600 mg of prednisone-equivalent during the month before diagnosis of PZ or IPA. Mixed pulmonary infection was considered to have occurred if there was a growth of ≥2 pathogens (excluding normal respiratory flora) in cultures of bronchoalveolar lavage (BAL) or sinus aspirate samples or in cultures of samples from a sterile site.

Image acquisition, selection, and interpretation. Day 0 of the study was defined as the day of onset of symptoms of PZ or IPA. The first CT scan that had been performed after the onset of each infection was evaluated in all cases. Chest CT scans had been obtained using either a LightSpeed QX/I scanner (General Electric Medical Systems) with 1.25-mm collimation (n = 4), 2.5-mm collimation (n = 3), or 3.75-mm collimation (n = 32) or a HiSpeed CT/I scanner with 7-mm collimation (n = 1). Nonionic contrast medium (120–150 mL Optiray 320; Mallinckrodt) had been injected in 32 patients via an antecubital vein at a rate of 3–4.2 mL/s with a 12–20-s delay.

The initial CT scans were reviewed in a blinded fashion by an experienced chest radiologist (E.M.M.). Pulmonary lesions were classified as (1) mass lesions, defined as >3-cm solid or consolidative nodules; (2) nodular lesions, including ≤3-cm solid or ground-glass nodular lesions that were further classified as macronodules (1–3 cm) or micronodules (<1 cm); or (3) air-space consolidation, including segmental and lobar consolidation and diffuse ground-glass opacities. Each lesion was further characterized for cavitation within the lesion, the halo sign (i.e., ground-glass opacities surrounding the solid portion of the nodule), the air-crescent sign (i.e., a crescent of air separating the central portion of the nodule from its wall), accompanying "tree-in-bud" opacities (i.e., tiny centrilobular nodules in a branching pattern indicative of fluid- or material-filled bronchioles), accompanying pleural effusion, and accompanying mediastinal or hilar adenopathy. The lobar location (upper, middle, or lower) and peripheral or central location of each lesion were also recorded. Lesions were considered to be peripheral of they were located within 3 cm of the pleura. The size of pleural effusion was graded as follows: small, occupying <25% of a hemithorax; moderate, occupying 25%–50% of a hemithorax; and large, occupying >50% of a hemithorax. The volume of each mass or nodular lesion was estimated by applying the formula volume = $\pi/6 \times$ height $\times$ length $\times$ width, as described elsewhere [13]. The length and width were measured on the axial CT slice that appeared to show the largest part of the nodule. The height of the nodule was calculated by subtracting the bed position from the first slice of the nodule from that of the last slice of the nodule.

Statistical analyses. We used the Mann-Whitney U test for analysis of continuous variables. Categorical data were analyzed with Fisher's exact test or the χ^2 test, as appropriate. A forward stepwise logistic regression analysis was performed for radiologic and clinical factors identified by univariate analysis, with a P value of ≤.2. ORs and 95% CIs were reported for all statistically significant variables ($P \le .05$). All analyses were performed with the Stata software program, version 8.0 (Stata).

RESULTS

Our search identified a total of 45 patients who had had either IPA or PZ; 16 consecutive patients had had PZ (9 had definite PZ, and 7 had probable PZ), and 29 patients had had IPA (8

had definite IPA, and 21 had probable IPA). All patients with IPA or PZ underwent bronchoscopy and BAL; sinus aspiration was performed for 5 patients with PZ who had associated sinus involvement. There were 6 additional patients with PZ who had mixed infection due to another mold (*Aspergillus* species in 5 patients and *Scedosporium apiospermum* in 1) who were excluded from the analysis. Five patients with PZ had concomitant sinus involvement, and 2 others had disseminated zygomycosis. The predominant Zygomycetes genus was *Rhizopus* (9 patients); there were also 2 patients infected with *Mucor* species. There were 11 patients with *Aspergillus fumigatus* infection, 6 with *Aspergillus flavus* infection, 5 with *Aspergillus terreus* infection, 4 *Aspergillus versicolor* infection, and 3 with *Aspergillus niger* infection. There was 1 case of definite and 3 cases of probable *A. versicolor* infection. In 5 patients with PZ and 2 patients with IPA, the diagnosis was established only by histopathological examination. The MIC_{50} values for voriconazole, itraconazole, amphotericin B, and caspofungin for the 11 Zygomycetes isolates available for susceptibility testing were 8.0, 4.0, 0.5, and >32 µg/mL, respectively. The MIC_{50} values for voriconazole, itraconazole, amphotericin B, and caspofungin for the 15 *Aspergillus* isolates available for susceptibility testing were 0.25, 1.0, 1.0, and 0.125 µg/mL, respectively. The MIC_{50} values for voriconazole, itraconazole, amphotericin B, and caspofungin for the 4 *A. terreus* isolates tested were 0.5, 1.0, 2.0, and 0.25 µg/mL, respectively.

As shown in table 1, patients in both groups were comparable in terms of underlying malignancy and most of the risk factors for IMIs (presence of GVHD, APACHE II score, malnutrition, and significant corticosteroid exposure) at the time of onset of infection. The vast majority of patients in both groups (15 [94%] of 16 with PZ and 27 [93%] of 29 with IPA) had hematological malignancies, and approximately one-half of the patients in each group were recipients of allogeneic BMTs (9 [56%] of 16 with PZ and 12 [41%] of 29 with IPA; $P = .36$). The presence of neutropenia at the time of the diagnosis was more common in patients with IPA (15 [51%] of 29 with IPA vs. 3 [19%] of 16 with PZ; $P = .05$), although within the month before diagnosis, neutropenia was seen with equal frequency in both groups (9 [56%] of 16 with PZ vs. 18 [62%] of 29 with IPA; $P = .74$).

Fever was the most common presenting sign among patients with PZ (63%) and those with IPA (69%), whereas facial pain or swelling was the only sign suggestive of PZ (25%, compared with 0% of patients with IPA; $P = .01$). Interestingly, symptoms that were considered to be specific to a pulmonary IMI, such as pleuritic chest pain (13% of patients with PZ vs. 10% of those with IPA) and hemoptysis (13% of patients with PZ vs. 14% of those with IPA), were uncommon in both patient groups. Concomitant sinus involvement ($P = .003$), receipt of voriconazole prophylaxis ($P = .005$), and diabetes mellitus

($P = .03$) were significantly associated with PZ in the univariate analysis (table 1). In the multivariate analysis, sinus involvement ($P = .026$), which was present only in patients with PZ, and receipt of voriconazole prophylaxis ($P = .003$) were the only independent clinical predictors of PZ (table 1).

Chest CT scans were available in 40 of the 45 patients in the study. Table 2 summarizes the CT findings. The timing of the initial CT from the onset of the infection was comparable in the 2 groups (median number of days from onset of infection to CT, 5 in the PZ group vs. 2 in the IPA group; $P = .25$), as were the use of intravenous contrast (69% for the PZ group vs. 88% for the IPA group; $P = .22$) and the collimation used (≤3.75 mm; 94% for the PZ group vs. 84% for the IPA group; $P = .63$). The presence of nodular opacities was the predominant CT finding in both patients with PZ (79%) and those with IPA (71%; $P = .83$). The peripheral distribution of nodules was also seen in the vast majority of patients with PZ (9 [82%] of 11) and IPA (17 [100%] of 17). However, the number of the nodules differed between the 2 entities. Thus, multiple nodules (≥10) were highly indicative of PZ (64% vs. 18%; $P = .02$). Additionally, micronodules (those <1 cm in size) were more commonly observed in the PZ group (6 [55%] of 11 vs. 3 [18%] of 17; $P = .09$) In contrast, mass lesions (i.e., nodular consolidations of ≥3 cm) found on CT scans were relatively uncommon in both groups (31% of subjects with PZ vs. 21% of those with IPA; $P = .48$). No differences were found between the 2 groups with regard to the diameter, volume, number, or location of mass lesions.

Similarly, air-space consolidations, cavitary lesions, and the halo sign were present in relatively low frequency among patients with PZ (38%, 25%, and 25% of patients, respectively) and those with IPA (29%, 17%, and 21%, respectively) The air-crescent sign was very uncommon; it was encountered in only 1 patient with PZ. Of note, opacities with a tree-in-bud appearance were observed more frequently among patients with IPA than among those with PZ (29% vs. 13%; $P = .11$). Finally, pleural effusions were more frequently observed among patients with PZ than among those with IPA (63% vs. 33%; $P = .1$). Pleural effusions were usually bilateral among patients with PZ (5 [50%] of 10) and those with IPA (6 [75%] of 8), and most of them were relatively small, occupying <25% of a hemithorax. The presence of multiple (≥10) nodules was the most powerful predictor of PZ in both univariate ($P = .002$) and multivariate analyses ($P = .012$) of the radiological parameters. The presence of pleural effusions was also independently associated with PZ in the multivariate analysis ($P = .042$).

DISCUSSION

Zygomycosis is an increasingly important IMI with a high crude mortality rate among both patients with hematological malignancies and BMT recipients [14]. The outcome of zygomycosis

has not improved substantially over the years [2, 4, 14]. Factors contributory to this continued poor response include the poor immune status of the hosts at risk for zygomycosis, the absence of new antifungal agents effective against Zygomycetes, and the delay in establishing the diagnosis [14]. Diagnostic challenges are further underscored by the fact that PZ, the dominant pattern of zygomycosis in immunocompromised patients, is frequently misdiagnosed initially as IPA. Despite the similarities in presentation of PZ and IPA in these patients, and despite the difficulties in establishing a definite diagnosis, no study has systematically compared these 2 entities. To our knowledge, this is the first study to compare clinical and radiological features of PZ and IPA with an aim of identifying possible characteristics with predictive value for PZ.

Table 1. Clinical characteristics of patients with pulmonary zygomycosis (PZ) and patients with invasive pulmonary aspergillosis (IPA).

Characteristic	Patients with PZ (n = 16)	Patients with IPA (n = 29)	Univariate analysis[a] OR (95% CI)	P	Multivariate analysis OR (95% CI)	P
Time to diagnosis after infection onset, median days (range)[b]	19 (4–103)	22 (0–120)	…	.34	…	
Age, median years (range)	48 (21–73)	57 (25–77)	…	.19	…	
Male sex	9/16 (56)	18/29 (62)	…	.75	…	
Hematological malignancy[c]	15/16 (94)	27/29 (93)	…	.58	…	
Active malignancy[d,e]	8/16 (50)	20/28 (71)	…	.20	…	
Receipt of an allogeneic BMT	9/16 (56)	12/29 (41)	…	.36	…	
Time to diagnosis after allogeneic BMT, median days (range)[e]	94 (24–601)	157 (20–1538)	…	.64	…	
Neutropenia[f]						
All cases[e]	3/16 (19)	15/29 (52)	4.64 (1.08–19.83)	.05	…	
≤30 days before diagnosis	9/16 (56)	18/28 (64)	…	.74	…	
Significant corticosteroid use[g]	11/16 (69)	15/29 (52)	…	.35	…	
History of diabetes mellitus	8/16 (50)	5/29 (17)	4.80 (1.21–18.98)	.03	…	
Malnutrition[e,h]	11/15 (73)	17/22 (77)	…	.35	…	
Active GVHD[i]	7/16 (44)	5/12 (42)	…	.78	…	
APACHE II score						
Median (range)	13.0 (8–24)	14.0 (5–23)	…	.78	…	
≥16	3/16 (19)	11/29 (38)	…	.31	…	
Sinus involvement	5/16 (31)	0/29 (0)	28.22 (1.44–553)	.004	25.73 (1.47–448.15)	.026
Shortness of breath[b]	6/16 (38)	15/29 (52)	…	.53	…	
Fever[b]	10/16 (63)	20/29 (69)	…	.74	…	
Nonproductive cough[b]	3/16 (19)	8/29 (28)	…	.72	…	
Pleuritic chest pain[b]	2/16 (13)	3/29 (10)	…	.78	…	
Hemoptysis[b,j]	2/16 (13)	4/29 (14)	…	.73	…	
Facial swelling[b]	4/16 (25)	0/29 (0)	21.24 (1.06–425)	.01	…	
Voriconazole prophylaxis[j]	9/16 (56)	4/29 (14)	8.03 (1.89–34.12)	.005	7.76 (1.32–45.53)	.023
Dose of voriconazole prophylaxis, median g (range)	10.8 (4.4–3.6)	21.2 (8.8–31.6)	…	.93	…	

NOTE. Data are no. of patients with characteristic/no. of patients with available data (%), unless otherwise indicated. BMT, bone marrow transplant; GVHD, graft-versus-host disease.

[a] At the onset of symptoms of PZ or IPA.

[b] Of the 15 patients with hematological malignancy and PZ, 5 had had acute myelogenous leukemia, 2 had acute lymphoblastic leukemia, 3 had had non-Hodgkin lymphoma, 2 had myelodysplastic syndrome, 2 had Hodgkin lymphoma, and 1 had chronic myelogenous leukemia. Of the 27 patients with a hematological malignancy and IPA, 11 had had acute myelogenous leukemia, 4 had had non-Hodgkin lymphoma, 5 had had acute lymphoblastic leukemia, 2 had had myelodysplastic syndrome, 2 had had chronic lymphoblastic leukemia, 2 had chronic myelogenous leukemia, and 1 had had Hodgkin lymphoma. Neither group included any patients with hemodialysis-dependent renal failure.

[c] Status of malignancy could not be assessed in 1 patient with IPA.

[d] At the time of diagnosis of PZ or IPA.

[e] Defined as a neutrophil count of <500 neutrophils/mm³.

[f] Defined as having taken >600 mg prednisone equivalent during the month before diagnosis of PZ or IPA.

[g] Active GVHD could be assessed in 15 patients with PZ and 12 with IPA. One patient with PZ who had active GVHD received anti-TNF treatment.

[h] Defined as an albumin level of ≤3 g/dL.

[i] Defined as a grade of III–IV. One patient with IPA had had massive hemoptysis and a fatal outcome.

[j] No differences were found between the PZ and IPA groups in terms of prophylaxis with amphotericin B, itraconazole, or caspofungin. Three and 2 patients with IPA received caspofungin or itraconazole prophylaxis, respectively; 3 and 1 patients with PZ received caspofungin or amphotericin B prophylaxis, respectively. None of the 5 patients with IPA due to *Aspergillus terreus* received amphotericin B prophylaxis.

Table 2. Radiological characteristics of patients with pulmonary zygomycosis (PZ) and patients with invasive pulmonary aspergillosis (IPA).

CT finding	Patients with PZ (n = 16)	Patients with IPA (n = 29)	Univariate analysis OR (95% CI)	P	Multivariate analysis OR (95% CI)	P
Time to initial CT scan after infection onset, median days (range)[a]	5 (−3 to 19)	2 (−4 to 18)	...	.25	...	
Nodules of ≤3 cm in maximum diameter[b]	11/14 (79)	17/24 (71)	...	.83	...	
Median no. of nodules (range)	11 (1–30)	3 (1–16)	...	.17	...	
≥10 Nodules present	7/11 (64)	3/17 (18)	8.16 (1.41–47.04)	.02	19.82 (1.94–202.29)	.012
Distribution						
Right lung	10/11 (91)	14/17 (82)	...	.93	...	
Left lung	9/11 (82)	11/17 (65)	...	.41	...	
Upper lobe	10/11 (91)	11/17 (65)	...	.19	...	
Lower lobe	7/11 (64)	13/17 (76)	...	.67	...	
Location						
Peripheral[c]	9/11 (82)	17/17 (100)	...	.14	...	
Central[c]	3/11 (27)	2/17 (12)	...	.35	...	
Diameter of nodule, median cm (range)	0.9 (0.4–3.0)	1.4 (0.1–2.7)	...	.62	...	
Micronodules[d]	6/11 (55)	14/17 (82)	...	.09	...	
Volume, median cm^3 (range)	0.36 (0.04–4.1)	1.68 (0.005–14.13)	...	.33	...	
Mass lesions of >3 cm in maximum diameter	5/16 (31)	5/24 (21)	...	.48	...	
Upper lobe distribution	3/5 (60)	2/5 (40)	...	1.0	...	
Peripheral location[e]	5/5 (100)	4/5 (80)	...	1.0	...	
Solitary mass	3/5 (60)	1/5 (20)	...	.52	...	
Mass diameter, median cm (range)	4.8 (3.8–5.8)	5.5 (1.6–6.6)	...	.66	...	
Mass volume, median cm^3 (range)	43.6 (21–87)	40.0 (2.1–93.9)	...	.93	...	
Total mass volume per case, median cm^3 (range)	52.8 (21–108)	69.4 (2.1–139.0)	...	.64	...	
Air-space consolidations[f]	6/16 (38)	7/24 (29)	...	.73	...	
Cavitations	4/16 (25)	4/24 (17)	...	.69	...	
Halo sign	4/16 (25)	5/24 (21)	...	.93	...	
Air-crescent sign	1/16 (6)	0/24 (0)	...	.40	...	
Ipsilateral hilar lymph nodes of ≥10 mm[g]	7/16 (44)	10/23 (43)	...	.54	...	
Pleural effusion[h]	10/16 (63)	8/24 (33)	...	.10	5.07 (1.06–24.23)	.042
Tree-in-bud opacities	2/16 (13)	7/24 (29)	...	.11	...	

NOTE. Data are no. of patients with characteristic/no. of patients with available data (%), unless otherwise indicated.

[a] From the onset of symptoms of PZ or IPA. A CT scan at the onset of disease symptoms was not available for 5 patients with IPA.

[b] Size of nodules could be assessed in 14 patients with PZ and 24 patients with IPA.

[c] In both patient groups, nodules were significantly more commonly distributed at the periphery of lungs (i.e., defined as within 3 cm of the pleura) than centrally (for IPA: OR, 217 [95% CI, 9.6–881; $P < .0001$]; for PZ: OR, 12 [95% CI, 1.6–91.1; $P = .03$]).

[d] Maximum diameter, ≤1 cm.

[e] In patients with PZ, mass lesions more frequently had peripheral (5 of 5) than central (1 of 5) location ($P = .04$).

[f] No differences in type and distribution of air-space consolidations were found between the 2 groups (data not shown).

[g] Two and 4 of 16 patients with PZ and 2 and 10 of 23 patients with IPA had bilateral and mediastinal lymph nodes, respectively. There were no differences between the PZ and IPA groups in the size and distribution of lymph nodes (data not shown).

[h] Pleural effusion was bilateral in 5 patients with PZ and in 6 patients with IPA ($P = .36$). In 7 of 10 patients with PZ and in 4 of 8 patients with IPA who had had pleural effusion, those effusions were <10% of lung volume (~1 L), as estimated on CT scans.

Not surprisingly, the vast majority of patients with either IPA or PZ had active hematological malignancies and a high prevalence of classic risk factors for IMI, including neutropenia, receipt of an allogeneic BMT, high-grade GVHD, significant corticosteroid exposure, and, frequently, malnutrition. However, certain clinical features did appear to favor the diagnosis of PZ. As we recently described, by comparing all patients with

zygomycosis (i.e., that not limited to the lungs) with contemporaneous patients with invasive aspergillosis, the presence of sinusitis and voriconazole prophylaxis were independently associated with the diagnosis of PZ [2].

Furthermore, we sought to identify radiological characteristics predictive of PZ as it compares to IPA at the onset of infection. Prior radiological studies of PZ included small case

series with mixed populations of mainly diabetic patients and subjects with cancer [10, 15–23]. Nonetheless, it is important to recognize that radiological manifestations of PZ differ between different host groups. For example, diabetic patients with PZ seem to have a high rate of endobronchial lung lesions [24]. Moreover, a majority of these studies analyzed plain chest radiographs and not CT scans [10, 18–20, 22]. However, the sensitivity of chest radiographs for detection of pulmonary fungal lesions is much lower than that for CT [11, 23]. Despite these limitations, most of these studies seem to suggest that PZ is associated with the presence of bulky nodular and cavitary lesions that have upper lung lobe predominance [10, 18–20].

In our study, the timing of CT scans from infection onset, a factor that significantly influences the type of lesions seen on CT [8, 13], was comparable in patients with PZ and those with IPA. In the logistic regression analysis of the CT findings, the presence of multiple nodules and, to a lesser degree, the presence of pleural effusions radiologically favored the presence of PZ. Additionally, micronodules seen on the initial CT scans were more commonly observed in patients with PZ. However, the reason for the predominance of these types of lesions in patients with PZ has no obvious pathophysiologic explanation. Although the incidence of cavitary and mass lesions in our series was similar to that in previous studies [10, 16–19], there was no difference in frequency of such lesions between patients with PZ and those with IPA. A peripheral distribution of mass or nodular lesions was observed in both patients with PZ and those with IPA. This observation may be explained by the fact that both *Aspergillus* species and Zygomycetes are angiotropic molds that invade blood vessels in the lungs, and, thus, the pulmonary lesions follow the vascular tracks to the lung periphery. Finally, our study emphasizes the association of tree-in-bud opacities with IPA, an infection that should certainly be included in the differential diagnosis of such lesions in severely immunocompromised patients [25].

Our study had several limitations, mainly its small size and retrospective nature. Also, the potential value of *Aspergillus* galactomannan antigen, a useful early diagnostic marker of IA [26], to distinguish patients with IPA from those with PZ was not assessed in the present study (the ELISA galactomannan assay was not available at our institution during the study period). Furthermore, because more than one-half of the cases in both groups were probable infections, firm conclusions are difficult to make. Finally, because our patients had unique host factors, one should be careful when applying these findings to other patient populations with different risk factors.

In summary, PZ is an emerging and frequently lethal IMI among heavily immunocompromised patients. There are no surrogate markers for early diagnosis of PZ, and therapeutic options are limited and frequently involve disfiguring surgery [4]. Early preemptive therapy with antifungals that have activity against Zygomycetes might be critical for improved outcome of patients with PZ. Additional prospective validation for the development of risk assessment models that could identify patients with early PZ, based on routine clinical and radiographic predictors, should be an important future direction of research.

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