Increasing Volume and Changing Characteristics of Invasive Pulmonary Aspergillosis on Sequential Thoracic Computed Tomography Scans in Patients With Neutropenia

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Purpose: **In patients with neutropenia, thoracic computed tomography (CT) halo and air-crescent signs are recognized as major indicators of invasive pulmonary aspergillosis (IPA). Nevertheless, the exact timing of CT images is not well known.**

Patients and Methods: **Seventy-one thoracic CT scans were analyzed in 25 patients with neutropenia with surgically proven IPA.**

Results: **On the first day of IPA diagnosis with early CT scan (d0), a typical CT halo sign was observed in 24 of 25 patients. At that time, the median number of thoracic lesions was two (range, one to six), and pulmonary involvement was bilateral in 12 cases. The halo sign was present in 68%, 22%, and 19% of cases on d3, d7, and d14, respectively. Similarly, the air-crescent sign was seen in 8%, 28%, and 63% of cases on the same days. Otherwise, a nonspecific air-space consolidation aspect was seen in 31%, 50%, and 18% of cases on the same days. The analysis of calculated aspergillary volumes on CT showed that, despite antifungal treatment, the median volume of lesions increased four-fold from d0 to d7, whereas it remained stable from d7 to d14. Overall, 21 patients (84%) were cured by the medical-surgical approach.**

Conclusion: **In patients with neutropenia, CT halo sign is a highly effective modality for IPA diagnosis. The duration of the halo sign is short, and it demonstrates the value of early CT. The increase of the aspergillosis size on CT in the first days after IPA diagnosis is not correlated with a pejorative immediate outcome when using a combined medical-surgical approach.**

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INVASIVE PULMONARY aspergillosis (IPA) remains a life-threatening complication in immunocompromised patients, especially in those with neutropenia.[1,2] Improvement of prognosis needs early recognition of IPA and effective antifungal treatment.[3,4] New approaches that use systematic thoracic computed tomography (CT) scan are useful for early documentation of IPA.[5,6] Nevertheless, the evolution of CT images and the changes in volume of visible disease during the course of IPA have been poorly studied. In patients with neutropenia, thoracic CT scan is a major tool for the diagnosis of IPA. Two CT signs are clearly identified as indicators of IPA. The CT halo sign is described as a mass-like infiltrate with a surrounding halo of ground glass attenuation. The halo lesion was shown to correspond to a central fungal nodule surrounded by a rim of hemorrhage and coagulative necrosis.[7] This halo sign is highly indicative of IPA and, it occurs early in the course of IPA, during the neutropenic period.[8-10] The air-crescent sign is described as a pulmonary cavitation. It is a later sign that appears with the bone marrow recovery.[9-11] This air-crescent sign is not pathognomonic of aspergillosis, but in the setting of leukemic patients, it is highly suggestive of filamentous fungal disease.[12] The present study analyzes the course of sequential thoracic CT scans performed in 25 patients with neutropenia with subsequently histologically proven IPA.

PATIENTS AND METHODS

Patients

Between October 1991 and March 1999, in the Department of Clinical Hematology, the diagnosis of IPA was established in 57 patients with hematologic malignancies. In 25 patients, the diagnosis was definitely proven after examination of a surgical tissue excision. Fifteen of these patients were included in a previous report.[6] Before the diagnosis was confirmed, the management of the 25 patients was identical in each case.

Management of Patients With Neutropenia With IPA Suspicion and Criteria for CT Scanning

In patients with neutropenia, the duration and severity of neutropenia are the major factors for the occurrence of IPA.[13] The occurrence of a febrile episode (most often a new episode in patients who received broad-spectrum antibiotics) or the identification of a chest x-ray

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infiltrate during prolonged neutropenia (usually > 2 weeks) triggered a CT scan. Some other features of IPA, such as chest pain or hemoptysis, were also recorded. A high-resolution CT scan (CT ProSpeed, General Electric, Fairfield, Conn) was used in all but one case with 10-mm thick sections and additional 1-mm thin sections through any suspected fungal lesions. A contrast enhancement was used when the aspergillary lesion threatened a pulmonary vessel. Because the scans were promptly performed when IPA was suspected, we defined the day of the first CT scan with halo sign evidence as the first day of IPA diagnosis (day 0). The medical therapy mainly relied on amphotericin B (AmB; Bristol-Myers Squibb, Paris, France), amphotericin B Lipid Complex (Abelcet; Wyeth Lederle Laboratories, Puteaux, France), liposomal amphotericin B (Ambisome; Nextar Laboratories, Paris, France), itraconazole (Janssen-Cilag Laboratories, Boulogne, France), or voriconazole (Pfizer Laboratories, Kent, United Kingdom). Subsequently, in cases in which IPA was thought likely, based on CT images and other data, sequential CT scans were performed during the following weeks to analyze the appearance and size of lesions. Usually, in the 24 hours after the first abnormal CT scan, a fiberoptic bronchoscopy with broncho-alveolar lavage (BAL) was performed, depending on the patient's condition.

Surgical Procedures and Definite Diagnosis of IPA

In all the cases described here, a definite diagnosis of IPA was achieved after examination of a tissue biopsy showing typical septate acute branching hyphae with or without positive culture for *Aspergillus*. The tissue biopsies were obtained by pulmonary surgical resection in all but one patient. The surgical procedures and indications were partially described in a previous report.[14] Briefly, the indications for pulmonary surgical resection of a suspected aspergillary lesion were as follows: (1) prevention of massive hemoptysis when IPA threatened integrity of pulmonary artery, (2) surgical reduction of a remaining *Aspergillus* mass before a new myeloablative treatment, and (3) open-lung tissue biopsy to confirm the IPA diagnosis.

Subsequent Review of Sequential Thoracic CT Scans and Determination of Aspergillary Volume

Each CT performed on day 0 and subsequently up to the day of surgical intervention was carefully reviewed by the radiologist (J.F.C.) in a blinded fashion and by the hematologist (D.C.). The parenchymal lesions were classified as follows: (1) nodular lesion surrounded by typical halo sign (Fig 1), (2) cavitated lesion described as typical CT air-crescent sign (Fig 2), (3) air-space consolidation or interstitial infiltrate with or without peripheral ground glass attenuation described as low or nonspecific images (Fig 3). It was hypothesized that each aspergillary lesion had an ovoid shape. Each lesion was measured in the two longer axes (length and width; anterior to posterior and right to left) at the CT section where the lesion was seen to be the biggest. The measure of the lesion height was obtained by using jointed CT sections. The calculated volume (in centimeters cubed) of each aspergillary volume was obtained using the following formula: volume = (height $\times$ length $\times$ wide $\times$ $\pi/6$). In cases of several aspergillary lesions, the total calculated volume of aspergillosis was obtained with the addition of each volume.

Statistical Analysis

The evolution of CT appearances and volumes of aspergillary lesions were compared using the Wilcoxon test and the Mann-Whitney *U* test as indicated.

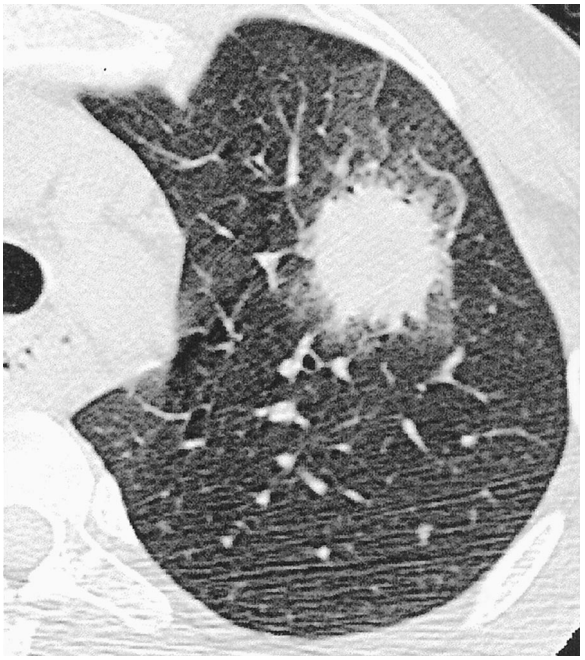

Fig 1. CT halo sign. This first thoracic CT scan (day 0) was performed in a patient with febrile neutropenic leukemia. The ground glass attenuation surrounding the nodule was considered a typical halo sign. The diagnosis of IPA was considered highly likely, and antifungal treatment was started.

RESULTS

Patients

Since October 1991, a definite diagnosis of IPA was achieved in 25 hematologic patients (median age, 52 years old; range, 5 to 65 years) after surgical resection of an aspergillary lesion. All the patients had received a myeloablative chemotherapy inducing neutropenia without bone marrow transplantation (BMT). Twenty-three patients (92%) had an acute leukemia. At the time of the IPA diagnosis, neutropenia had been present for a median length of 19 days (range, 11 to 28 days) and 12 patients (48%) had progressive hematologic disease (failure or relapse).

Initial Diagnosis of Aspergillosis

Clinical signs associated with IPA included fever greater than 39°C in 84% of patients and chest pains in 60%. An episode of hemoptysis (most often minor) occurred in 39% of patients.

Because the diagnosis of IPA was suspected, a first thoracic CT scan was performed promptly in 24 of 25 patients. In all of these cases, this first CT showed at least one typical halo sign with the classic image of nodule surrounded by ground glass attenuation. In one case, the presumed diagnosis of IPA was based on the evidence of

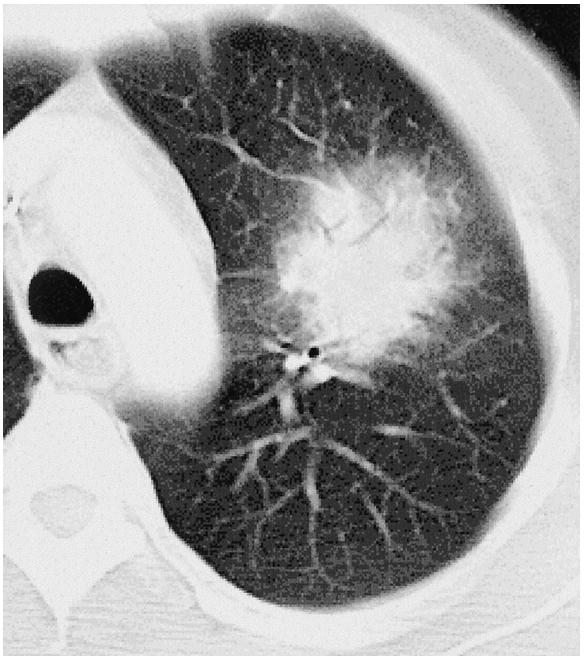

Fig 2. Low specific CT image. A new CT scan was performed 4 days later (day 4). It showed an increase of the left-sided aspergillary mass with a partial loss of peripheral ground glass attenuation.

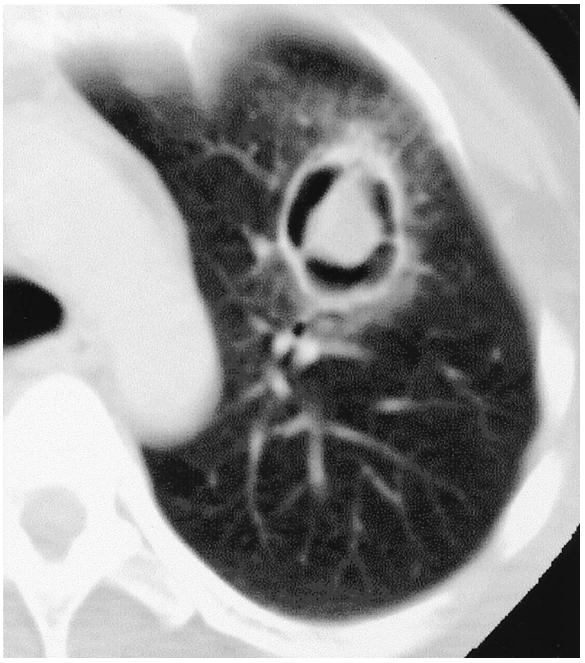

Fig 3. CT air-crescent sign. Marrow recovery occurred on day 7. On day 10, an air-crescent sign appeared on CT scan. A surgical resection confirmed the diagnosis of IPA. Subsequently, the patient received itraconazole for 12 months, and 30 months later, she was well and alive.

Aspergillus in the BAL combined with bilateral infiltrate on x-ray and the first CT was performed 12 days later, showing two cavitary lesions with air-crescent signs. Overall, on the first CT performed, the median number of aspergillary lesions was two (range, one to six) and pulmonary involvement was bilateral in 12 (48%) of 25 cases.

A BAL was performed in 18 patients. In five cases (28%), culture and/or direct examination of BAL were positive for *Aspergillus*. A latex *Aspergillus* antigen test (Pastorex Aspergillus, Sanofi Diagnostics, Pasteur, France) was identified as positive in BAL fluid from 13 (76%) of 17 examined cases. Interestingly, antigen was positive in 9 of 13 cases with negative culture of BAL.

Aspergillus antigenemia was measured on repeated serum samples in all of the patients. A latex agglutination test was performed in 20 patients and was found positive in nine patients. In 16 patients, *Aspergillus* antigenemia was measured with an enzyme-linked immunoadsorbent assay test (Platelia Aspergillus, Sanofi Diagnostics), and it was found positive in 11 patients.

Medical Antifungal Therapy

As soon as the presumed diagnosis of IPA was established, the antifungal treatment was initiated or changed. At the time of IPA diagnosis, 16 patients were already receiving intravenous conventional AmB (for febrile mucositis in most cases) for a median time of 9 days at a median daily dose of 1 mg/kg. In nine of these 16 cases, AmB was stopped. Twenty-one patients were treated with itraconazole (median dose, 400 mg/d; median duration, 300 days) either alone (six cases) or in combination (15 cases). It was combined with AmB (median dose, 1 mg/kg/d; median duration, 10 days) in 10 cases. Itraconazole was associated with Abelcet (four cases) or Ambisome (one case; median dose, 5 mg/kg/d; median duration, 19 days). Four patients were treated with voriconazole (median dose, 6 mg/kg/d; median duration, 63 days).

Evolution of CT Appearances and Aspergillary Volumes

The characteristics of CT evolution are summarized in Table 1. Overall, before surgery, 71 thoracic CT scans (median number of CTs per patient, three; range, one to four) were performed in the 25 patients. In 24 cases, a CT scan was performed early after occurrence of IPA (day 0), and a typical CT halo sign was observed in all of the cases. Subsequently, 47 sequential CT scans were obtained at day 3 (range, two to five), day 7 (range, days 6 to 10), and day 14 (range, days 11 to 19) after IPA diagnosis. At days 0, 3, 7, and 14, the incidence of CT halo sign was 100%, 68%, 22%, and 19%, respectively. The first image of CT air-

Table 1. Characteristics of 71 Sequential Thoracic CT Scans in 25 Patients With IPA

	Day 0		Day 3		Day 7		Day 14	
	No. of Patients/ Total	%	No. of Patients/ Total	%	No. of Patients/ Total	%	No. of Patients/ Total	%
Time after IPA diagnosis, days								
Median	0		3		7		14	
Range	0-0		2-5		6-10		11-19	
No. of CT scans performed	24		13		18		16	
Patients with typical thoracic CT halo sign	24/24	100	8/13	68	4/18	22	3/16	19
Patients with low- or nonspecific thoracic CT images	none		4/13	31	9/18	50	3/16	18
Patients with typical thoracic CT air-crescent signs	none		1/11	8	5/18	28	10/16	63
Calculated volume of aspergillary lesions, cm^3								
Median	11		37		47		34	
Range	0.1-57		9-119		4-167		2-202	

crescent sign appeared at day 3 in one case (8%), and then it was observed at days 7 and 14 with a 28% and 63% incidence, respectively. The frequency of CT scans with low or nonspecific images (eg, air-space consolidation) at days 3, 7, and 14 was 31%, 50%, and 18%, respectively. The main result of this analysis was that the CT halo sign was a transitory sign (duration less than 5 days in most cases). Moreover, during the second week of the course of the aspergillosis, in most cases, CT scans were not helpful for diagnosis as the features were nonspecific. The appearance of the air-crescent sign was correlated with an increase of the peripheral polymorphonuclear cell count (from median value $0/mm^3$ [range, 0 to $200/mm^3$) at day 0 to $2,850/mm^3$ [range, 0 to $11,000/mm^3$] at day 14). Therefore, the air-crescent sign occurred too late to be interesting for an early diagnosis of IPA. The evolution of the thoracic aspergillary volume was calculated for each patient (Table 1 and Fig 4). From day 0 to day 3, the volume increased significantly (approximately three-fold; $P = .002$, Wilcoxon test). From day 0 to day 7, the volume increased significantly (approximately four-fold; $P = .0005$, Wilcoxon test). Lastly, from day 0 to day 14, the volume increased approximately three-fold ($P = .009$, Wilcoxon test). Conversely, the volume remained stable between day 7 and day 14 ($P = .6$, Wilcoxon test). No influence in changing volume was found according to the different antifungal treatment.

Surgery and Definite Diagnosis of IPA

The median time between IPA diagnosis and surgery was 18 days (range, 2 to 46 days). Twenty-four patients underwent a pulmonary surgical resection either as a therapeutic procedure (19 cases) or as a diagnostic procedure (five cases). Thirteen patients underwent an emergency pulmonary resection (despite persistent granulocytopenia in nine cases) to prevent life-threatening hemoptysis. The need for surgical intervention was based on observation of repeated chest CT scans showing pulmonary aspergillosis that was in immediate proximity to the pulmonary artery. A lobectomy was practiced in all but one case. A delayed elective surgery was practiced in the remaining 10 patients. Six patients underwent a surgical resection of a pulmonary residual mass before a new hematologic treatment, whereas surgery was performed as a diagnostic procedure in four patients. In one patient, the diagnosis of IPA was achieved with a postmortem open-lung biopsy. Lastly, one patient (with concomitant pulmonary involvement of lung and brain) underwent a surgical resection of a brain abscess. In all of the cases, histopathologic analysis revealed invasion of the tissue by acute angle branching septate hyphae. The culture of the tissue biopsy grew *Aspergillus* in 17 of 24 performed cases.

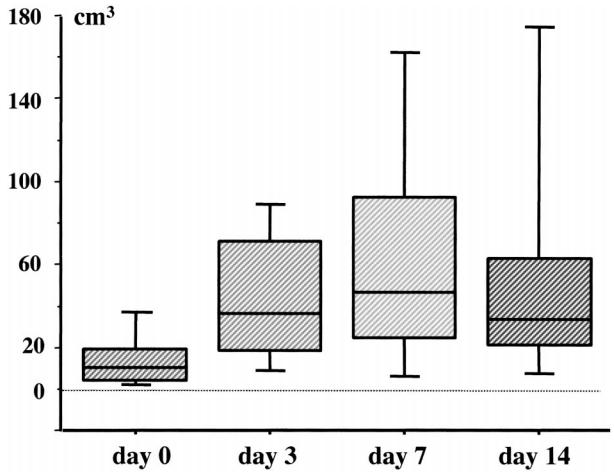

Fig 4. Evolution of the thoracic aspergillary volume. From day 0 to days 3, 7, and 14, the volume significantly increased approximately three- to four-fold ($P < .01$). Conversely, the volume remained stable between day 7 and day 14 ($P = .6$).

Clinical Outcome

Four patients (16%) in hematologic failure died from IPA with a median delay of 45 days (range, 13 to 90 days) after diagnosis. Twenty-one patients (84%) were improved or cured by antifungal treatment combined with surgery. The initial volume of aspergillary lesions at day 0 was similar in the group of patients who died from aspergillosis and in the other group (Mann-Whitney *U* test). Overall, the median duration of survival after IPA diagnosis was 526 days (range, 130 to 1,936 days) in the cured patients group. In 17 of these 21 patients, a complete hematologic response was achieved. Subsequently, 15 patients received new myeloablative therapies (including two autologous and two allogenic BMTs) without progression of IPA.

DISCUSSION

Because pulmonary aspergillosis remains a life-threatening complication for immunocompromised patients, one problem is to establish a presumptive diagnosis of IPA as soon as possible. In the present series, aside from CT characteristics, the evidence supporting the diagnosis of IPA was limited or absent. Fever is a too common problem in patients with neutropenia to be considered a warning sign of aspergillosis. Prolonged and profound neutropenia is a crucial risk factor for the occurrence of aspergillosis.[13] The main clinical indicators of aspergillosis associated with prolonged neutropenia were chest pains and hemoptysis, which were observed with a frequency of 60% and 36%, respectively.[15,16] Nevertheless, these later signs are not pathognomonic of IPA. In patients with neutropenia, the combination of a positive culture of BAL for *Aspergillus* and the presence of new pulmonary infiltrates is tantamount to a confirmed diagnosis of IPA.[4,17,18] Nevertheless, in our series, the culture of BAL remained negative in 70% of cases. Moreover, in all but one case, BAL was performed after the first evidence of IPA on CT scan. Serum tests for IPA in patients with neutropenia mainly relied on the *Aspergillus* antigenemia.[19] In our study, as in other reports, the detection of *Aspergillus* antigenemia with the Platelia Aspergillus test was better (but not perfect) than the Pastorex Aspergillus test to suspect a diagnosis of IPA.[19,20] Conversely, we found that the detection of *Aspergillus* antigen on BAL with the Pastorex Aspergillus test was useful (76% positive). In this report, the thoracic CT scan was the tool of choice to achieve the earliest and most likely diagnosis of pulmonary aspergillosis in patients with neutropenia. Previous studies reported that the thoracic CT scan might be helpful in the diagnosis of pulmonary aspergillosis.[5-10] Initially, the value of the CT halo sign as an indicator of IPA was described by Kuhlman et al.[5,8] According to these preliminary results, numerous authors acknowledged the value of the CT halo sign as a highly predictive sign of IPA in patients with neutropenia.[9-11] The image occurs early in the disease and allows the assumption of aspergillosis before the typical cavitation.[5,8-11] Therefore, we assigned major diagnostic importance to CT scans and, in particular, to the halo sign. Since the end of 1991, we have successfully used the thoracic CT scan in the management of patients with febrile neutropenia.[6] In the present series of surgically proven aspergillosis, it seems that when CT scan is systematically and promptly performed in patients with febrile neutropenia at risk of aspergillosis, its positive predictive value is almost 100%. Nevertheless, the duration of this halo sign is short. Three quarters of the initial CT halo signs disappeared within a week after IPA diagnosis. To be useful for IPA diagnosis, the CT scan must be performed early in the course of the disease and probably in the first 5 days after the occurrence of the disease (Table 1). This fact could explain the lower incidence of halo signs in the same settings in other reports.[9-11] When CT was delayed for a few days, nonspecific images (mainly air-space consolidations) were seen and were not helpful for IPA diagnosis. In the present series, 50% of CT scans performed between day 6 and day 10 showed these nonspecific appearances (Table 1). Finally, when CT was delayed for 2 weeks, the incidence of halo decreased to fewer than 20% of cases and the air-crescent sign appeared in 63% of cases. Although this air-crescent sign was highly indicative of pulmonary aspergillosis, it was too delayed to be useful in the early management of IPA. As in other reports, we found that the occurrence of the air-crescent sign was strongly correlated with bone marrow recovery.[16] Overall, in a patient with neutropenia at risk of invasive aspergillosis (at least 2 weeks of deep neutropenia), the timing of the evolution of the IPA could be roughly described as a 3-week development. The first week allows the achieving of an early IPA diagnosis with CT halo evidence, whereas the second week is mainly silent for diagnosis with nonspecific CT aspects and the third week could be considered as a late confirmation of diagnosis with evidence of air-crescent sign. However, our experience is almost exclusively based on patients undergoing chemotherapies for leukemia without allogenic BMT. In these later patients, the occurrence of aspergillosis is most often delayed after bone marrow engraftment and probably related to severe immunosupression.[21,22] In the setting of allogenic BMT, Ribaud et al[22] reported an incidence of 60% of halo signs in IPA screened with CT. However, some authors question the value of the halo sign as major indicator of IPA.[23,24] In the report of Primack et al,[23] four of 12 patients with CT halo signs did not have any pulmonary infectious processes. However, these four pa-

tients were not immunocompromised. Conversely, in accordance with our results, Blum et al[10] did not find any false-positive value for halo signs, while they experienced a 100% specificity rate and a 72% sensitivity rate when CT scans were performed in the first 2 weeks of the disease.

In our series, the systematic study of the sequential CT scans in patients with neutropenia with definite IPA allowed us to determine the exact timing of CT images and the evolution of the aspergillary mass during the course of the disease. The major point of the volume study is that despite early initiation of medical antifungal therapy, the volume of the thoracic aspergillary lesions systematically increased in the first days of the disease. Indeed, the calculated volume of IPA increased approximately three- to four-fold between day 0 and median day 7. Subsequently, the volume of IPA did not significantly change. The apparent failure of the antifungal agents in the first weeks of the medical therapy encourages the idea that the cure of aspergillosis needs other means to be achieved. Our antifungal therapy choice mainly relied on azoles, as in some other reports.[4,25,26] Although the lipidic formulations of AmB seem to be promising, the number of our patients treated with them was too small to be evaluated.[27] The hematologic response is probably the major help to cure IPA.[6] In this report, the four patients who died from aspergillosis were in hematologic failure, whereas 17 of 21 patients successfully treated were in complete hematologic response. The use of surgery could be helpful to facilitate the improvement of IPA, in this report as well as in others.[14,28-30] The surgery allows decreasing of the volume of aspergillary mass. In the case of single aspergillary focus, it could be a curative procedure. In this later case, it facilitates the further myeloablative therapies and especially the realization of allogenic BMT.[14,29,30] In this report, we achieved a 84% rate of success in the treatment of patients with neutropenia with IPA. It seems to be superior to rates in other reports in which IPA treatment mainly relied on a medical approach.[2,4,25-27] Therefore, in a medical-surgical approach, the initial radiologic progression of the disease is not systematically correlated with a worse prognosis.

In conclusion, in the patients with neutropenic at risk of invasive aspergillosis the systematic use of thoracic CT scans seems to be the best way to achieve an early and probably specific diagnosis of IPA when the CT halo sign is observed. Nevertheless, the shortness of halo appearance on CT requires its systematic and prompt use when IPA is suspected. Moreover, the CT scan allows the observation of the evolution of the aspergillary disease and the determination of the exact timing of the surgery if necessary. In the setting of an early assisted CT scan IPA diagnosis combined with a medical-surgical approach, the prognosis of IPA remains favorable despite the initial apparent failure of antifungal therapy.

REFERENCES

1. Bodey G, Bueltmann B, Duguid W, et al: Fungal infections in cancer patients: An international autopsy survey. Eur J Clin Microbiol Infect Dis 11:99-109, 1992

2. Denning DW, Stevens DA: Antifungal and surgical treatment of invasive aspergillosis: Review of 2121 published cases. Rev Infect Dis 12:1147-1201, 1990

3. Fisher BD, Armstrong D, Yu B, et al: Invasive aspergillosis. Progress in early diagnosis and treatment. Am J Med 71:571-577, 1981

4. Denning DW, Lee JY, Hostetler JS, et al: NIAID Mycoses Study Group: Multicenter trial of oral itraconazole therapy for invasive aspergillosis. Am J Med 97:135-144, 1994

5. Kuhlman JE, Fishman EK, Burch PA, et al: Invasive pulmonary aspergillosis in acute leukemia: The contribution of CT to early diagnosis and aggressive management. Chest 92:95-99, 1992

6. Caillot D, Casasnovas O, Bernard A, et al: Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. J Clin Oncol 15:139-147, 1997

7. Hruban RH, Meziane MA, Zerhouni E, et al: Radiologic-pathologic correlation of the CT halo sign in invasive pulmonary aspergillosis. J Comput Assist Tomogr 11:534-536, 1987

8. Kuhlman JE, Fishman EK, Siegelman SS: Invasive pulmonary aspergillosis in acute leukemia: Characteristic findings on CT, the CT halo sign, and the role of CT in early diagnosis. Radiology 157:611-614, 1985

9. Potente G: Computed tomography in invasive pulmonary aspergillosis. Acta Radiol 30:587-590, 1989

10. Blum U, Windfuhr M, Buitrago-Tellez C, et al: Invasive pulmonary aspergillosis: MRI, CT, and plain radiographic findings and their contribution for early diagnosis. Chest 106:1156-1161, 1994

11. Mori M, Galvin JR, Barloon TJ, et al: Fungal pulmonary infections after bone marrow transplantation: Evaluation with radiography and CT. Radiology 157:605-610, 1991

12. Funada H, Misawa T, Nakao S, et al: The air crescent sign of invasive pulmonary mucormycosis in acute leukemia. Cancer 53:2721-2723, 1984

13. Gerson SL, Talbot GH, Hurwitz S, et al: Prolonged granulocytopenia: The major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. Ann Intern Med 100:345-351, 1984

14. Bernard A, Caillot D, Couaillier JF, et al: Surgical management of invasive pulmonary aspergillosis in neutropenic patients. Ann Thorac Surg 64:1441-1447, 1997

15. Gerson SL, Talbot GH, Hurwitz S, et al: Discriminant scorecard for diagnosis of invasive pulmonary aspergillosis in patients with acute leukemia. Am J Med 79:57-64, 1985

16. Albelda SM, Talbot GH, Gerson SL, et al: Pulmonary cavitation and massive hemoptysis in invasive pulmonary aspergillosis. Influence of bone marrow recovery in patients with acute leukemia. Am Rev Respir Dis 131:115-120, 1985

17. Albelda SM, Talbot GH, Gerson SL, et al: Role of fiberoptic bronchoscopy in the diagnosis of invasive pulmonary aspergillosis in patients with acute leukemia. Am J Med 76:1027-1034, 1984

18. Kahn FW, Jones JM, England DM: The role of bronchoalveolar lavage in the diagnosis of invasive pulmonary aspergillosis. Am J Clin Pathol 86:518-523, 1986

19. Verweij PE, Stynen D, Rijs AJ, et al: Sandwich enzyme-linked immunosorbent assay compared with Pastorex latex agglutination test for diagnosing invasive aspergillosis in immunocompromised patients. J Clin Microbiol 33:1912-1914, 1995

20. Caillot D, Cuisenier B, Vagner O, et al: *Aspergillus* antigen detection by latex agglutination or sandwich ELISA in invasive pulmonary aspergillosis in neutropenic patients. Am Soc Microb 37th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Canada, September 28-October 1, 1997

21. Cordonnier C, Bernaudin JF, Bierling P, et al: Pulmonary complications occurring after allogenic bone marrow transplantation. A study of 130 consecutive transplanted patients. Cancer 178:721-726, 1985

22. Ribaud P, Chastang C, Latge J-P, et al: Survival and prognostic factors of invasive aspergillosis after allogenic bone marrow transplantation. Clin Infect Dis 28:322-330, 1999

23. Primack SL, Hartman TE, Lee KS, et al: Pulmonary nodules and the CT halo sign. Radiology 190:513-515, 1994

24. Won HJ, Lee KS, Cheon JE, et al: Invasive pulmonary aspergillosis: Prediction at thin-section CT in patients with neutropenia—A prospective study. Radiology 208:777-782, 1998

25. De Beule K, De Doncker P, Cauwenbergh G, et al: The treatment of aspergillosis and aspergilloma with itraconazole, clinical results of an open international study (1982-1987). Mycoses 31:476-485, 1988

26. Denning D, Del Favero A, Gluckman E, et al: UK-109,496, a novel, Wilde-spectrum triazole derivative for the treatment of fungal infections: Clinical efficacy in acute invasive aspergillosis. Am Soc Microb 37th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 17-20, 1995

27. Walsh TJ, Hiemenz JW, Seibel NL, et al: Amphotericin B lipid complex for invasive fungal infections: Analysis of safety and efficacy in 556 cases. Clin Infect Dis 26:1383-1396, 1998

28. Wong K, Waters CM, Walesby RK: Surgical management of invasive pulmonary aspergillosis in immuno-compromised patients. Eur J Cardiothorac Surg 6:138-143, 1993

29. Moreau P, Zahar JR, Milpied N, et al: Localized invasive pulmonary aspergillosis in patients with neutropenia: Effectiveness of surgical resection. Cancer 72:3223-3226, 1993

30. Reichenberger F, Habicht J, Kaim A, et al: Lung resection for invasive pulmonary aspergillosis in neutropenic patients with hematologic diseases. Am J Respir Crit Care Med 158:885-890, 1998