Role of early diagnosis and aggressive surgery in the management of invasive pulmonary aspergillosis in neutropenic patients

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Invasive pulmonary aspergillosis (IPA) occurs mostly in immunocompromised hosts and especially in neutropenic patients. Improved prognosis for IPA requires early diagnosis. We report our experience in the management of IPA in patients with hematological malignancies. In prolonged neutropenia (>10 days), thoracic CT scanning seems to be the best choice for the diagnosis of IPA (with CT halo or air-crescent signs). Its systematic use allows a dramatic reduction in the time to achieve the diagnosis, if there is evidence of a halo sign. The systematic screening for the detection of \textit{Aspergillus} antigenemia with an ELISA test is helpful for early diagnosis. The detection of \textit{Aspergillus} antigen (with the less sensitive latex agglutination test) on bronchoalveolar lavage (BAL) fluid may also be as useful. The treatment of IPA relies on amphotericin B (or its lipid formulations) or on azole antifungal agents. Pulmonary surgical resection should be considered either as an emergency procedure (despite persistent neutropenia) to avoid massive hemoptysis, or as an elective or diagnostic procedure. This global strategy for the management of IPA is associated with a 75–80% success rate in hematological patients. Nevertheless, the control of underlying malignancy remains a major prognostic factor.

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INTRODUCTION

Invasive aspergillosis remains a life-threatening complication in immunocompromised patients, especially in neutropenic patients, and its incidence has increased in such patients during the past two decades [1–3]. The prognosis remains poor in leukemic patients, despite amphotericin B (AmB) treatment. The mortality rate reaches 60–65% when invasive pulmonary aspergillosis (IPA) occurs during chemotherapy-induced neutropenia and could exceed 90% in the setting of allogeneic bone marrow transplantation (BMT) [4,5]. IPA is the most common form (>80–90% of cases) of the disease, especially in neutropenic patients [5,6]. Some reports demonstrate that early recognition of IPA and prompt antifungal treatment could improve the prognosis [7,8].

Since 1992, we have used a global strategy for the management of IPA in hematological patients. This approach includes the following: (1) early, high resolution thoracic CT scanning; (2) systematic screening of \textit{Aspergillus} antigen in serum and broncho-alveolar lavage (BAL) and plasma fibrinogen concentration; (3) early initiation of antifungal treatment, combined with aggressive pulmonary surgery if necessary. Here, we present the results of this approach, which has dramatically improved the prognosis for IPA in our neutropenic patients [9,10].

PATIENTS

Between January 1988 and July 2000, we managed 1579 episodes of bone marrow aplasia in patients with hematological diseases. The clinical approach and management of febrile neutropenia during this period was essentially unchanged. Microbiological monitoring included a daily blood culture and samples from the throat, nose, urine and stool weekly. Axillary temperature was measured every 3 h. When the first febrile episode occurred, a beta-lactam antibiotic plus aminoglycoside were used as empirical therapy after microbiological sampling and a chest X-ray. When fever persisted, a glycopeptide was added at 48 h. AmB was administered (0.7–1.0 mg/kg per day) if the fever persisted for 24–48 h following the addition of glycopeptide or in the case of a subsequent...
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febrile episode in a patient with ongoing neutropenia. Since 1992, in addition to this clinical strategy, we have made a systematic search for IPA in our neutropenic patients.

A pneumonia was identified in 279 cases. A diagnosis of IPA was made in 86 patients (mean age, 53 ± 17 years; male/female ratio, 1.26). As in other reports, most patients (84%) had acute leukemia and the incidence of IPA was 5.5% [2,3,11,12]. Seven patients had a multiple myeloma, as previously reported [13]. As described by Gerson, the main risk factor of IPA occurrence was the length and severity of neutropenia [14]. In our series, all but one of the patients were neutropenic at the time of IPA diagnosis and the median duration of previous neutropenia (PMN < 100/mm³) was 19 days (range, 8-43). The other risk factors were identified either as T-cell depletion in two allo BMT patients or progressive hematological disease in 52% of our patients [5,11,12,15]. Because 90% of IPA occurred in patients hospitalized in rooms not protected by laminar airflow, the effect of air filtration on preventing aspergillosis during neutropenia was good but not perfect [5,16].

CLINICAL SIGNS OF IPA

Fever is too common a problem in neutropenic patients and should not be considered as an indicator of aspergillosis [17]. However, in our experience, 87% of the patients who developed IPA had fever above 39 °C in the days before IPA diagnosis. The other recognized clinical indicators of IPA are chest pain and hemoptysis [18,19]. We observed these indicators with a frequency of 64% and 36%, respectively.

VALUE OF THORACIC CT SCAN FOR IPA DIAGNOSIS

Thoracic CT signs of IPA in neutropenic patients

In neutropenic patients, thoracic CT scanning is an important tool for the diagnosis of IPA. Two CT signs have been clearly identified as indicators of IPA. The CT halo sign (Figure 1) is described as a mass-like infiltrate with a surrounding halo of ground glass attenuation. It corresponds to a central fungal nodule surrounded by a rim of hemorrhage and coagulative necrosis [20]. Initially, the value of the CT halo sign as an indicator of IPA was described by Kuhlman et al. [21,22]. According to these preliminary results, numerous authors have acknowledged the value of the CT halo sign as a highly predictive of IPA in neutropenic patients [23-25]. The air-crescent sign (Figure 2) is described as a central cavitation. It is a later sign that appears with the bone marrow recovery [25,26]. This air-crescent sign is not pathognomonic of aspergillosis but, in the case of patients with hematological malignancies, it is highly suggestive of filamentous fungal disease [26,27]. Therefore, we assigned major diagnostic importance to CT scans and, in particular, to the halo sign. Thus, the occurrence of a febrile episode (most often a new episode in patients receiving broad-spectrum antibiotics) or the identification of a chest X-ray infiltrate during prolonged neutropenia (usually >2 weeks) called for a CT scan. A high-resolution CT scan was used with 10-mm-thick sections and additional thin (1-mm) sections through any suspected fungal lesions. Contrast enhancement was used when the aspergillar lesion threatened a pulmonary vessel.

Impact of systematic use of CT scan in neutropenic patients

Since 1992, we have successfully used thoracic CT scanning in the management of febrile neutropenic patients [9].
Before 1992, 13 cases of IPA were diagnosed and chest CT scans were used only to document aspergillosis in eight patients (most often, after the diagnosis of IPA was made by other methods). In only one of the eight patients, the CT scan was the first evidence of IPA (with the presence of the halo sign). Since 1992, all the 73 remaining patients had at least one CT scan. Among these later patients, an early diagnosis of IPA (with evidence of the CT halo sign) was achieved in 68 patients (93%). An earlier diagnosis of IPA was the result of their approach (Table 1). The median time between the first clinical sign and IPA diagnosis (retrospectively determined on fever, cough or chest pain occurrences) was significantly shortened from 9 days (range, 0–17) before 1992 to 1 day (range, 0–5) since 1992 (P = 0.0001; Mann–Whitney U-test). During the same time, we have observed a reduction in IPA-related mortality from 2.5% to 1.3% (P = 0.008; Fisher’s exact test) (Table 1 and Figure 3).

Evolution of CT images during IPA in neutropenic patients

To assess the value of thoracic CT scans in IPA diagnosis, we have retrospectively analyzed 71 sequential thoracic CT scans in 25 neutropenic patients with surgically proven IPA [28]. This study demonstrated that, in a neutropenic patient at risk for invasive aspergillosis (at least 2 weeks of deep neutropenia), the evolution of the IPA lesions could be observed over a 3-week period. In the first week, the halo sign is present, while the second week usually exhibits nonspecific changes (Table 2). In the third week, the air-crescent sign appears and may be helpful as a late indicator of IPA. The major point of these observations is that the duration of the halo sign is short (less than 5 days in most cases). Therefore, to be useful for IPA diagnosis, the CT scan must be performed very early in the course of the disease.

Our experience is based exclusively on patients undergoing chemotherapies for leukemia without allogenic BMT. It agrees with the work of Blum et al., who described a 100% specificity rate and a 72% sensitivity rate of the halo sign when CT scans were performed in the first 2 weeks of the disease [24]. In allogeneic BMT patients, aspergillosis most often occurs after bone marrow engraftment, probably secondary to severe immunosuppression [29,30]. In the case of allogeneic BMT, Ribaud reported an incidence of 60% of the halo sign in IPA in patients who had a CT scan [30]. However, some authors question the value of the halo sign as an important indicator of IPA [31,32]. In the report of Primak et al., four of 12 patients with the CT halo sign did not have any pulmonary infection [31]. However, these four patients were not immunocompromised. Overall, we think that the systematic use of thoracic CT scans is the best way to achieve an early diagnosis in neutropenic patients.

BIOLICAL DIAGNOSIS OF IPA

Detection of Aspergillus antigenemia

Two tests are currently available for the detection of circulating galactomannan. In neutropenic patients, the latex

![Figure 3 Impact of early diagnosis of IPA on the outcome. Kaplan–Meier survival curves according to the strategy for IPA diagnosis and therapy. Since 1992, progress in early diagnosis (e.g. CT scan, Aspergillus antigenemia detection) combined with a medical-surgical approach were associated with improved survival of IPA patients.](Image)

Table 1 Contribution of CT-scans, Aspergillus antigenemia detection and surgery for the management of IPA in neutropenic patients

<table>
<thead>
<tr>
<th></th>
<th>Before 1992</th>
<th>Since 1992</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>IPA observed (n)</td>
<td>13</td>
<td>73</td>
<td>NA</td>
</tr>
<tr>
<td>Patients with thoracic CT scans (n)</td>
<td>8/13 (62%)</td>
<td>73/73 (100%)</td>
<td>&lt;0.0001**</td>
</tr>
<tr>
<td>CT scan with suggestive halo-sign before IPA diagnosis (n)</td>
<td>1/8 (13%)</td>
<td>68/73 (93%)</td>
<td>&lt;0.0001**</td>
</tr>
<tr>
<td>Prospective detection of Aspergillus antigenemia with an ELISA test</td>
<td>0/13 (0%)</td>
<td>35/73 (48%)</td>
<td>0.0005**</td>
</tr>
<tr>
<td>Pulmonary surgery combined with medical treatment</td>
<td>0/13 (0%)</td>
<td>26/73 (36%)</td>
<td>0.006**</td>
</tr>
<tr>
<td>Mean time</td>
<td></td>
<td></td>
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<tr>
<td>Admission to hospital–IPA diagnosis (days)</td>
<td>31 ± 8</td>
<td>21 ± 5</td>
<td>0.0005*</td>
</tr>
<tr>
<td>First IPA signs–IPA diagnosis (days)</td>
<td>7.4 ± 5</td>
<td>1.6 ± 1.3</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Death attributed to IPA (n)</td>
<td>7/13 (54%)</td>
<td>13/73 (18%)</td>
<td>0.008**</td>
</tr>
</tbody>
</table>

IPA, invasive pulmonary aspergillosis; NA, not applicable. *Mann–Whitney U-test; **Fisher’s exact test.
agglutination test (Pastorex Aspergillus, Sanofi Diagnostics Pasteur, France) appears to be highly specific but not very sensitive [5,33]. In our experience, about one-third of patients with IPA tested by Pastorex Aspergillus were positive [34]. However, the test was never positive before IPA diagnosis. The use of the sandwich ELISA test (Platelia Aspergillus<sup>6</sup>; Sanofi Diagnostics Pasteur, France) increases the sensitivity (about 15–20-fold) of Aspergillus antigenemia but is not perfect [5,33]. In a prospective multicenter study (using twice-weekly detection of antigenemia in neutropenic patients at risk for IPA), we have found the sensitivity and specificity of the ELISA test to be 50% and 97% respectively [35]. In the same study, the positive and negative predictive values were 60% and 80%, respectively, and one-third of the patients had a positive antigen test before the diagnosis of IPA by CT scanning [35].

**Interest of BAL**

Fiberoptic bronchoscopy with BAL should be performed if IPA is suspected. However, the level of positivity of direct examination and culture does not exceed 30–50% [5,6,36]. In neutropenic patients, the combination of a positive culture of BAL for *Aspergillus* and the presence of new pulmonary infiltrates are tantamount to a confirmed diagnosis of IPA [37]. In our treatments, 74 of 86 patients with IPA underwent a BAL. Direct examination and/or culture were positive in 46% of cases. Conversely, we found that the detection of *Aspergillus* antigen on BAL supernatant with the Pastorex Aspergillus<sup>6</sup> test was useful (42/59 positive results). Moreover, in 42 IPA patients with positive detection of *Aspergillus* antigen on BAL fluid, 20 had a negative culture for *Aspergillus*. To assess the value of detection of *Aspergillus* antigen on BAL, we conducted a prospective study on 139 consecutive BAL performed on patients with (n = 61) or without (n = 78) hematological malignancies. Among the nonhematological patients, no false-positive result was found. In the hematological patients, the sensitivity and specificity of the test were 67% and 89% respectively [38]. Therefore, in a febrile neutropenic patient with X-ray infiltrates or suggestive CT signs, the positivity of *Aspergillus* antigen in the BAL fluid could have the same value as the isolation of *Aspergillus* in the BAL. The isolation of *Aspergillus* in expectorated sputum or from a nasal swab should be taken into account when diagnosing aspergillosis in leukemic patients [39]. In our experience, the diagnosis of IPA was most often established when positive results were available.

**Value of fibrinogen level**

In our neutropenic patients, the fibrinogen level is systematically measured on alternate days during hospitalization. In our 86 IPA patients, fibrinogen increased from a median value of 4.5 (range, 1.8–8.1) at day–10 before IPA diagnosis to a median value of 7 g/L (range, 4.1–11.4) at the day of IPA diagnosis (mostly with the CT halo sign). In the setting of prolonged neutropenia, the fibrinogen value was also a prognostic factor, because a fibrinogen value higher than 9 g/L was associated with a negative outcome. Specific receptors for fibrinogen have been identified on the surface of *A. fumigatus conidia* and they could act as mediators of conidial adherence to host tissue [40]. However, it remains impossible to know whether fibrinogen increase is the cause or the consequence of the progression of IPA.

**LEVEL OF CONFIDENCE OF IPA DIAGNOSIS (TABLE 3)**

**Definite and highly probable diagnosis of IPA**

Historically, a definite diagnosis of IPA required histopathological evidence of tissue invasion with hyphae morphologically consistent with *Aspergillus* species [6]. Using this definition, a positive culture was not necessary. In our experience, 36 patients had histologically proven IPA. Considering the high value of CT halo or air-crescent signs in neutropenic patients, we think that the combination of positive CT signs and either a positive culture of BAL or positive detection of *Aspergillus* antigen on BAL should also be
considered as definite IPA. In our series, 35 patients exhibited such criteria for IPA. Clinical, radiological and serological features of these later patients did not differ from those with histologically proven IPA. Overall, 71 of 86 IPA cases (83%) were considered as definite.

**Probable or possible diagnosis of IPA**

Among the remaining neutropenic patients at risk for IPA (neutropenia = 10–15 days), we classified aspergillosis as probable or possible. A probable diagnosis of IPA required (in addition to appropriate clinical features) the presence of the CT halo sign combined with the detection of circulating galactomannan (=1.5 ng/mL) with the ELISA test (Platelia Aspergillus®). A possible diagnosis of IPA was only based on the presence of the CT halo sign. Nine patients exhibited criteria for probable and six for possible IPA. The comparison of the sequential evolution of CT images (with initial evidence of CT halo signs and secondary occurrence of CT air-crescent signs) between the definite or highly probable IPA and probable or possible IPA did not show any differences. The sequence of halo then air-crescent signs was observed in 42 of 66 cases in the first group vs. 10 of 15 in the second group (P = 0.23; Fisher’s exact test).

**MEDICAL ANTIFUNGAL TREATMENT OF IPA**

The traditional treatment of aspergillosis in immunocompromised patients is AmB [4–6]. In leukemic patients, especially in allogenic BMT patients, the efficacy of AmB was limited, with a failure rate ranging from 50% to 90% [4,5]. The recent introduction of new triazole agents (itraconazole or voriconazole) or new formulations of AmB (amphotericin B lipid complex, amphotericin B colloidal dispersion or liposomal amphotericin B) appears to improve the prognosis of pulmonary aspergillosis in hematological patients. The response rate with these newer drugs is reaching about 50% [41–48]. In our experience, therapy mainly relied on these available drugs. Among our 86 IPA patients, 32 were treated with a single agent: itraconazole, 19 cases; voriconazole, eight cases; AmB, five cases. Thirty-nine received a combination of two antifungal agents: AmB and itraconazole, 28 cases; lipidic formulations of AmB and itraconazole, 11 cases. The remaining 15 patients were treated with an AmB preparation, followed by an azole. The efficacy of these different approaches was globally similar (with a 77% success rate). The median duration of antifungal therapy was approximately 6 months for the responding patients.

**SURGICAL MANAGEMENT OF IPA**

The surgical procedures and indications for surgery have been partially described in previous reports [10,11]. Briefly, the indications for pulmonary surgical resection of a suspected aspergillary lesion are 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; (3) open lung tissue biopsy to confirm the IPA diagnosis.

In immunocompromised patients with IPA, and especially in neutropenic patients, massive hemoptysis represents a 10–15% cause of death [49]. The angiotropism of Aspergillus could explain the mechanism of hemoptysis. During the neutropenic period, following chemotherapy, the hyphae colonize the bronchi and the arteries, and cause local infarction [50]. When marrow recovery occurs, the granulocyte count increases and proteolytic enzymes are released from leukocytes at the site of aspergillary infection. This might cause destruction of lung tissue [51]. In the setting of IPA located near a pulmonary artery (or its dividing branches), it might cause massive hemoptysis by arterial perforation. Therefore, the recovery of the granulocyte count is a critical period [19,49]. In our experience, three of 13 neutropenic patients with IPA (observed before 1992) presented with severe hemoptysis when marrow recovery occurred. Two patients died, while one underwent successful bronchial artery embolization.
Therefore, when IPA threatened the integrity of the pulmonary artery, we hypothesized that preventive surgical resection of the fungal lesion (before bone marrow recovery) might reduce the risk of death related to arterial perforation. In our institution, 14 patients underwent emergency pulmonary resection (despite persistent granulocytopenia and thrombocytopenia in 10 and 11 cases respectively) to prevent life-threatening hemoptysis. The need for surgical intervention was based on the observation of repeated chest CT scans showing pulmonary aspergillosis that was in immediate proximity to the pulmonary artery (Figure 2). A lobectomy was performed in all but one case.

Delayed surgery could be helpful in facilitating the improvement of IPA, as others have described [52-54]. Resection surgery decreases the volume of the remaining aspergillar mass. In the case of single aspergillar foci, it could be curative. In this later case, it facilitates the further myeloablative therapies and, in particular, subsequent allogenic BMT [52,53]. We have carried out delayed elective surgery in 12 patients. Seven patients underwent surgical resection of a pulmonary residual mass before the next course of hematological treatment, while surgery was undertaken as a diagnostic procedure in five patients.

Overall, among our 26 surgical patients, the main criteria of IPA diagnosis before surgery were based on CT findings (alone or combined with antigen test on BAL fluid) in 81% of cases. A definite diagnosis of IPA was achieved histologically in all these patients. Moreover, the analysis of sequential thoracic CT scans performed before surgery (Table 2) showed that the volume of the aspergillar lesions typically increased 3-4-fold in the first week of the disease [28]. Despite this initial apparent failure, we achieved an 84% rate of success in the treatment of IPA with this surgical approach [28]. Therefore, in a medical-surgical approach, the initial radiological progression of the disease is not usually correlated with the prognosis.

OUTCOME AND PROGNOSTIC FACTORS

In our experience, 66 of 86 (77%) neutropenic patients with IPA were improved or cured. Currently, the median survival of responding patients is 393 days after IPA diagnosis (range, 103-3683). These results seem to be superior to other reports of IPA treatment which mainly relied on a medical approach [4,37,41-48].

Since 1992, we have initiated a systematic and global strategy of IPA management in neutropenic patients. The main results of this diagnostic and therapeutic strategy were a reduction in the time required for diagnosis (more than 1 week since 1992) and an improvement in the rate of survival. The effect of an earlier diagnosis of IPA was associated with a better prognosis of the disease (46% of patients observed before 1992 survived more than 100 days after IPA diagnosis vs. 82% since this date; Figure 3).

In addition, in a univariate analysis model (log-rank test), we have found several significant factors associated with a better prognosis:

- the achievement of a complete hematological response with recovery of neutropenia (P < 0.0001);
- the occurrence of an air-crescent sign on CT scanning, which follows marrow recovery (P < 0.0001);
- a maximum fibrinogen level of < 9 g/L in the 10 days after IPA diagnosis (P < 0.0001);
- initial unilateral involvement of the lung by IPA (P = 0.02);
- combined surgical and medical therapy (P = 0.05);

In an multivariate analysis (Cox model), three poor prognostic factors were found to be significant (Figure 4):

- a fibrinogen level = 9 g/L during the 10 days after IPA diagnosis (P = 0.003);
- the absence of the CT air-crescent sign during IPA evolution (P = 0.0004);
- initial bilateral involvement of the lung by IPA (P = 0.01).

CONCLUSION

Although pulmonary aspergillosis in neutropenic patients remains a life-threatening complication of myeloablative therapy, a global strategy for diagnosis and therapy could greatly improve its prognosis. Early IPA diagnosis could be achieved with careful daily clinical monitoring, systematic use of CT scans, detection of Aspergillus antigenemia (and plasma fibrinogen level) and detection of Aspergillus antigen on BAL fluid (in addition to culture). The main goal of this diagnostic strategy is to initiate antifungal treatment as soon as possible.

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Moreover, a surgical approach should be considered if necessary (either as an emergency procedure to prevent a massive hemoptysis before marrow recovery or as an elective procedure after neutropenia resolution). Nevertheless, the control of underlying hematological disease remains one of the factors for improvement.

REFERENCES


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