ORIGINAL ARTICLE

Invasive pulmonary aspergillosis in patients with acute leukemia

Aspergillose pulmonaire invasive chez les patients atteints de leucémie aigue

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Abstract

Introduction: Invasive pulmonary aspergillosis is a serious complication in hematology.
Aim: Describe the prevalence, diagnostic aspects, therapeutic modalities, and evolution of the IPA cases occurring in patients with acute leukemia.
Methods: Our study was retrospective including patients with acute leukemia who developed invasive pulmonary aspergillosis during the period January 2009 and December 2020 at the hematology department in south Tunisia. The IPA was defined in three levels of probability according to the criteria of the EORTC / MSG 2019.
Results: We collected 127 patients who presented with Invasive pulmonary aspergillosis. Sixty-three percent of our patients had acute myeloid leukemia. The diagnosis of invasive pulmonary aspergillosis was during the induction course in 76% of cases. Twenty-seven of our patients had chest pain. The chest Computed tomography (CT) scan showed the Halo sign in 89% of cases. The Aspergillus galactomannan antigen was positive in 38% of cases. Extrapulmonary aspergillosis involvement was noted in 18% of cases: IPA was possible and probable respectively in 59% and 41% of cases. All patients treated with Voriconazole with a favorable response in 54% of cases. The mortality rate was 46%. The overall survival at week 12 was 56%.
Conclusion: The morbidity and mortality of patients who developed invasive pulmonary aspergillosis with acute leukemia in our series were high. We need to improve our strategy for early diagnosis and management.

Key words: Invasive pulmonary aspergillosis, acute leukemia, epidemiology, diagnosis, voriconazole.

Résumé

Introduction: L'aspergillose pulmonaire invasive est une complication redoutable en hématologie.
Objectif: Décrire les aspects diagnostiques, thérapeutiques et évolutives de l'aspergillose pulmonaire invasive chez les patients atteints de leucémies aigues.
Méthodes: Notre étude rétrospective a concerné les patients atteints d'une leucémie aiguë, suivis au service d'hématologie du Sud Tunisien, et ayant présenté une aspergillose pulmonaire invasive durant la période janvier 2009 et Décembre 2020. L'aspergillose pulmonaire invasive était définie en trois niveaux de probabilité selon les critères de l'EORTC/MSG 2019.
Résultats: Nous avons colligé 127 patients. Soixante-trois pourcent de nos patients avaient une leucémie aiguë myéloïde. Le diagnostic de l'aspergillose pulmonaire invasive était retenu dans 76% des cas au cours de la cure d'induction. Vingt-sept patients avaient des douleurs thoraciques. Le scanner thoracique a montré le signe de Halo dans 89% des cas. L'antigène galactomannane d'Aspergillus était positif chez 38% de nos patients. Une atteinte extra-pulmonaire de l'aspergillose a été notée dans 18% des cas. L'aspergillose pulmonaire invasive était possible et probable respectivement dans 59% et 41% des cas. Tous les patients ont été traités par Voriconazole avec une réponse favorable dans 54% des cas. Le taux de mortalité liée à l'aspergillose pulmonaire invasive était de 46%. La survie globale à la 12ème semaine était de 56%.
Conclusion: La morbidité et la mortalité des patients ayant une aspergillose pulmonaire invasive et atteints de leucémie aigüe dans notre série était élevée. Une amélioration de notre stratégie s`impose pour un diagnostic et une prise en charge précoce.

Mots clés: aspergillose pulmonaire invasive, leucémie aiguë, épidémiologie, diagnostic, voriconazole.

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Introduction

Invasive pulmonary aspergillosis (IPA) is the most serious fungal infection in patients with hematological malignancies mainly in patients with acute leukemia (AL)(1) . The incidence of invasive aspergillosis has increased in such patients during the past two decades. Despite the therapeutic advances, the prognosis of IPA remains poor and its treatment remains difficult (2). The mortality rate of IPA exceeds 50% in immunocompromised patients (3) . Improved prognosis for IPA requires a better standardization of diagnostic but also therapeutic and preventive approaches. The management of IPA has many problems at the hematology department of Southern Tunisia because of the difficulty of the diagnosis, and the cost of treatment. Few studies have been reported regarding this infection in our country (4,5).

Aim: Describe the prevalence, diagnostic aspects, therapeutic modalities, and evolution of the IPA cases occurring during the treatment of patients with AL.

Methods

This study retrospectively analysed all patients with acute leukemia who have been treated by chemotherapy with IPA at Hedi Chaker Hospital, Sfax, Tunisia, from January 2009 to December 2020. The inclusion criteria were: (1) patients with a diagnosis of AL (myeloblastic or lymphoblastic) by morphology or flow cytometry reports; (2) age older form 2 to 65 years; (3) patients receiving intensive chemotherapy. The exclusion criteria were all patients with AL under palliative care.

We collected epidemiological, clinical, biological, therapeutic, and outcome data for each patient. The available mycological tests were analyzed at the Department of Parasitology–Mycology University Hospital-Sfax, Tunisia. The serum aspergillus galactomannan antigen was performed once a week in all patients. The test was considered positive if it had a value greater than 0.5 ng/ml using the ELISA technique on 2 successive tests a few days apart. The performance of polymerase chain reaction (PCR) for aspergillus on blood is unsystematic. A PCR of Aspergillus as well as a direct examination and culture on broncho-alveolar lavage fluid (BAL) were performed if patients underwent BAL. A chest X-ray and or chest computed tomography (CT) were performed in all febrile patients on broad-spectrum antibiotic therapy. The IPA diagnostic criteria followed are those of the European Organization for Research and Treatment of Cancer / Mycoses Study Group (EORTC / MSG) revised in 2019 (6). The IPA is defined in three levels of probability according to the criteria related to the host, the clinical criteria, and the mycological criteria of the EORTC / MSG 2019. IPA is considered possible in case of the presence of a host-related factor and clinical criteria. IPA is considered probable in the presence of a host-related factor, microbiological criteria, and major clinical criteria. Proven IPA is defined by the demonstration of aspergillus filaments in diseased tissue or from a sterile site or by the detection of DNA aspergillus (6–7). Patients treated with Voriconazole when the IPA is possible or probable or proven at doses adapted to age and weight according to the recommendations of the IDSA 2008 (8). The combination Voriconazole + Amphotericin B or Caspofungin was prescribed for refractory forms of IPA. The therapeutic response was evaluated according to the criteria of the EORTC / MSG 2008 as a complete response if resolution of all clinical signs and disappearance of more than 90% of CT lesions due to IPA, a partial response if clinical improvement and improvement of more than 50% of CT lesions and a stable response if stability or less than 50% improvement in CT lesions (9). Treatment failure was considered if the clinical symptoms were worsening and the computed tomography lesions worsened (9).

The data from each sheet were entered using the Statistical Package for Social Sciences software, SPSS Statistics 20, which was used to calculate the different statistical parameters studied. Categorical variables are expressed as frequencies and percentages and non normally distributed continuous variables are expressed as medians with interquartile ranges (IQR). Overall survival was calculated based on the Kaplan-Meier study.

Results

One hundred and twenty-seven cases of IPA over 660 cases of AL were enrolled during the 12-year study period with an average annual recruitment of 11 cases. The prevalence of IPA over cases of AL and AML was 19% and 13%. The epidemiological and biological characteristics of our patients are shown in Table 1.

Table 1. Epidemiological and biological characteristics of patients

Patients	Number of patients (%)
Sex	
Male	72 (57)
Female	55 (43)
Acute leukemia	
Lymphoblastic	47 (37)
Myeloblastic	80 (63)
Therapeutic phase	
Induction	96 (76)
Salvage therapy	9 (7)
Consolidation	21 (17)
Neutropenia	
<200 elts/mm^3	98 (77)
200-499 elts/mm^3	15 (12)
>500 elts/mm3	14 (11)
High doses of Dexamethasone	
≥ 6 mg/m^2/day ≥ 14 days	39 (30)

Eighty patients (63%) had acute myeloid leukemia (AML) and 47 patients were diagnosed with ALL. The median age of our patients was 32 years (range, 3 - 64 years). The sex ratio was 1.3. The diagnosis of IPA developed during chemotherapy induction in 76% of cases. The mean time between chemotherapy initiation and diagnosis of IPA was 21 days (extremes of 1 to 59 days). Thirty-nine patients (30%) were treated with high doses of Dexamethasone. One hundred thirteen patients (89%) had deep neutropenia (neutrophils count <0.5 elements/109). All our patients were febrile on broad-spectrum antibiotics at the time of IPA diagnosis. Cough was noted in 79% of patients respectively. Twenty-four

patients (19%) had dyspnea, 27 patients (21%) had chest pain and 3 patients (2%) had hemoptysis (table 2).

Table 2. Pulmonary signs in patients with IPA

Clinical signs	Number of patients (%)
Fever	127 (100)
Cough	100 (79)
Dyspnea	24 (19)
Chest pain	27 (21)
Hemoptysis	3 (2)

Chest X-ray was pathological in 27% of cases. Chest CT scan was performed in all patients with a delay of 1 to 10 days from the onset of respiratory symptoms. The sign of Halo isolated or associated with other radiological signs was present in 89% of cases. Other radiological signs such as condensation, excavation, and nodules were found in 14 % of cases (Table 3).

Table 3. Radiological scanner images in patients with IPA

Radiological images	Number of patients (%)
Isolated halo sign	43 (34)
Halo sign + condensation	36 (28)
Halo sign + excavation	6 (5)
Halo sign + nodule	28 (22)
Condensation	12 (9)
Excavation	2 (2)
Total	127 (100)

Galactomannan antigen done for 100 patients (78%) was positive in 38% of cases. Therefore, BAL was performed in only 19% of cases and direct examination and bronchial fluid culture were positive for aspergillus flavus in 2 patients. PCR of aspergillus, performed in 3 patients (on the bronchial fluid in 1 patient and on blood sample in 2 patients), was positive in all 3 patients. According to the EORTC/MSG (2019) criteria, the IPA was classified as possible and probable respectively in 59% and 41% of cases (Table 4).

Table 4. The distribution of patients according to the level of certainty of IPA according to EORTC/MSG criteria (2019)

IPA certainty level	Number of de patients (%)
Possible	
Clinical criteria + radiology	61 (48)
Clinical criteria + antigenemia	14 (11)
Probable	
Clinical criteria + radiology + antigenemia	52 (41)
Proved	
Clinic + radiology + antigenemia + direct examination + anatomopathology	0
Total	127 (100)

No patient had a proven IPA. Extra-pulmonary aspergillosis developed in 23 patients (18%) with a sinus localization in 6% of cases (Table 5).

All patients were treated with Voriconazole. The median duration of treatment with Voriconazole was 90 days (range:1 to 20 months). Fourteen patients had received a combination of antifungal agents for a refractory IPA. The number of patients who could be evaluated after one month of treatment was 116. Eleven patients died before evaluation because of progression of leukemia. Complete therapeutic response was noted in 35% of all treated cases, partial response in 19%, stability in 7%, and failure in 39%. The causes of death of patient AL with IPA included respiratory failure in 12 cases and septic shock in 10 cases. The Overall survival rate at 12 weeks was 56% (Figure1).

Table 5. Extra pulmonary aspergillosis localization

Aspergillosis localization	Number of cases (%)
Hepatosplenic	**10 (8)**
Naso-Sinus	**7 (6)**
Cerebral	**1 (1)**
Muscular	**1 (1)**
Digestive	**1 (1)**
Cutaneous	**1 (1)**
Ocular	**1 (1)**
Total	**23 (18)**

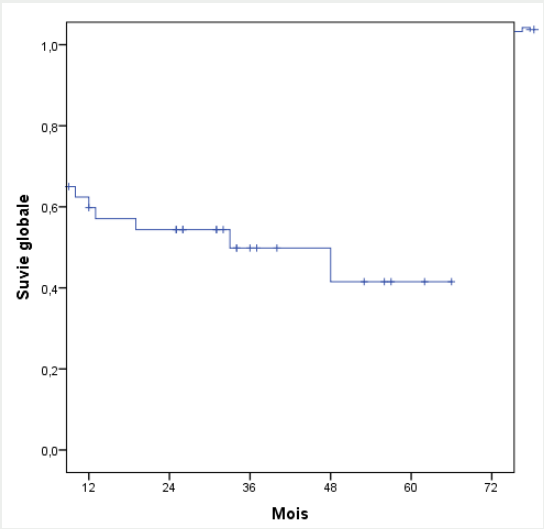

Figure 1. Overall survival in patient with IPA

Mortality in our patient AL with IPA was related to aspergillosis in 46% and to leukemia progression in 9%. Discussion: IPA has negative impact on the survival of our patient with acute leukemia related to difficult diagnosis as clinical signs are often unspecific which delay treatment. The frequency of IPA in acute leukemia (AL) patients in our series was higher (19%) than that reported in the previously described incidence rates in Tunisia and in the literature (5% to 15%) explained by the lack of air filtration room and the absence of anti-fungal prophylaxis (4,5,10). From 2005, the frequency of IPA was reduced with the antifungal prophylaxis in hematology in developed countries (11). IPA developed more in patients with AML than with ALL in our study and in the literature (12) because of the deep and prolonged neutropenia induced by chemotherapy during the AML treatment (12) . The addition of high doses of corticosteroids is the major risk factor for IPA in lymphoblastic forms in our study as in the literature (10). Early symptoms are cough and fever, constant in our study as well as in the literature (13). Dyspnea, noted in 19% of our patients, is most often a late sign, indicating the extension of lung lesions. Approximately 25% to 33% of immunocompromised patients initially have no symptoms attributable to IPA (13). The most characteristic sign of IPA is localized

or diffuse chest pain corresponding to the infarction of the sub-pleural cortical parenchyma. Hemoptysis, rarely described in our study and in the literature (2%), is a sign of parenchyma invasion seen in the advanced form of aspergillosis (13). Extra-pulmonary aspergillus localizations can be hepato-splenic, naso-sinus, cerebral, digestive, muscular, cutaneous, cardiac, ocular and bone damage (14). Hepato-splenic localization is more frequent in our series (table 5) than in the literature (13). The overall sensitivity and specificity of serum aspergillus antigenemia for the diagnosis of IPA is 60-80% and 84-95% respectively (15,16). Positivity of serum aspergillus antigenemia was noted in 38% of our patients. Aspergillus antigenemia is also of interest for the monitoring and prognosis of IPA (16,17). The use of PCR is reduced in our series as well as in the literature due to the lack of standardization of the results obtained. PCR methods could be useful, after standardization, in association with the detection of antigens (18,19). The presence of aspergillus filaments on a bronchial aspiration of a neutropenic patient suspected of pneumopathy is a strong argument for an IPA. The sensitivity of direct examination and culture exceeds rarely 50%. The BAL is an invasive and difficult examination to perform in patients with post-chemotherapy aplasia. It has been performed in one-third of our patients only because of severe thrombocytopenia. The Aspergillus flavus, found in 3 cases only (2%), is the most frequent agent in our ecology as shown in a study by Hadrich. I et al (5). In contrast, in the literature, distal BAL is positive in 50 to 70% of cases, and the most frequent causative agent is Aspergillus fumigatus (19). Halo's sign is the most frequent CT radiological sign in our study as well as in the literature (20,21). It corresponds to a perilesional hemorrhage and generally occurs very early in the evolution of IPA and disappears in a few days. In Caillot et al study involving 37 patients monitored in hematology, a CT scan was systematically performed in all febrile neutropenic patients, which revealed the halo sign in 92% of cases at an early stage, reducing the diagnostic delay from 7 days to 2 days (20). However, this sign is not specific to an IPA and may be described in other fungal infections (candidiasis, coccidioidomycosis), bacterial diseases (tuberculosis, Pseudomonas infection), viral infections (cytomegalovirus, myxovirus or herpes virus infection), or no infectious conditions (Wegener's disease, Kaposi's sarcoma, broncho-alveolar carcinoma, non-Hodgkin's lymphoma, metastasis, pulmonary embolism) (22). However, in an at-risk patient, the existence of a halo surrounding a pulmonary condensation or nodule should be the first criteria of a possible IPA diagnosis and treatment should be initiated without delay. The diagnosis of IPA is based on EORTC/MSG (2019) (7) criteria: host-related criteria, microbiological criteria: BAL, aspergillus antigenemia, polymerase chain reaction (PCR), detection of aspergillus DNA and major clinical criteria (radiological lesions on chest CT). According to the EORTC/MSG 2019 criteria, we find more cases of possible IPA in our series (59%) as well as the literature (82%) (10), this is explained by the lack of mycological criteria in favor of aspergillosis. Proven IPA is still under-estimated in our series as well as in the literature by the difficulty of the histological test or positive culture due to the frequent presence of severe thrombocytopenia in these patients.

According to recommendations from both IDSA and ECIL and the French Consensus Conference, Voriconazole is the first-line treatment of choice in IPA(23). This treatment has been available in Tunisia since 2008. A favorable overall response was obtained in 42% of the cases in our study. The efficacy of Voriconazole in the treatment of IPA in the 1st line has been well demonstrated in several studies with a response ranging between 43-48% (18). The superiority of Voriconazole in first-line treatment compared to conventional Amphotericin B has been well demonstrated in several studies in terms of efficacy, safety, response (52.8 vs. 31.6%), and 12-week survival (71% vs. 58%) (24). Several randomized and non-randomized studies have shown the value of new classes of antifungal agents (Caspofungin, Posaconazole, Itraconazole, Ravuconazole) as monotherapy or in combination with Voriconazole or Ambisome® in the treatment of refractory IPA (23). The combination of Caspofungin and Ambisome® or Voriconazole is associated with a better response (25). Caspofungin-ambisome® or Caspofungin-Voriconazole combination is associated with a better response rate than Caspofungin monotherapy (18). The 2nd line treatment of IPA in patients considered refractory to Voriconazole in our series was based on a combination of Amphotericin B® and Voriconazole in the majority of our patients due to the high cost of Caspofungin and the unavailability of other classes of antifungal agents. The evolution was unfavorable for all these patients.

Despite therapeutic progress, the prognosis for invasive aspergillosis remains poor. IPA re-mains a life-threatening complication in immunocompromised patients, especially neutropenic patients and it is associated with high mortality both in our series (39%) and in the literature (30% to 60%) (26).

The improvement in the prognosis of IPA is related, on the one hand, to advances in early
diagnostic tools and, on the other hand, the introduction of antifungal agents, in particular Voriconazole alone or in combination.

Conclusion

The IPA is a frequent complication during the treatment of AL especially in AML and it's associated with the high mortality rate in our study. Other strategies, including early diagnosis, anti-fungal prophylaxis, the performance of aspergillus antigen twice a week, and installation of an air filtration unit are needed for improving assessment and therapeutic results of IPA among AL patients.

Abreviations list:

IPA: Invasive pulmonary aspergillosis
AL: Acute Leukemia
PCR : polymerase chain reaction
BAL: broncho-alveolar lavage fluid
CT: chest computed tomography
AML: acute myeloid leukemia

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