DISSEMINATED INVASIVE ASPERGILLOSIS WITH CEREBRAL INVOLVEMENT IN LEUCEMIC PATIENT

ASPERGILLOSE DISSEMINEE AVEC ATTEINTE CEREBRALE CHEZ UN PATIENT LEUCEMIQUE

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Résumé :

Nous rapportons un cas d'aspergillose invasive (AI) disséminée avec atteinte cérébrale chez un homme de 57 ans atteint d'une leucémie aiguë lymphoblastique. Des signes respiratoires sont apparus à 40 jours après l'instauration de la chimiothérapie. Trois jours après, le patient a présenté des convulsions, une hémiparésie gauche et un ictère cutanéo-muqueux. L'imagerie a montré des signes évocateurs d'AI disséminée avec atteinte pulmonaire, cérébrale, maxillaire et probablement hépatique. Aspergillus niger a été isolé dans les crachats à quatre reprises et l'antigénémie aspergillaire s'est révélée positive. Le patient a été traité avec de l'amphotéricine B puis avec du voriconazole et a bénéficié d'un drainage chirurgical de son abcès cérébral. L'évolution a été favorable pendant deux ans durant lesquels le patient est resté en rémission hématologique. Puis, il est décédé suite à la rechute de sa leucémie.

Mots clés : Aspergillose invasive, abcès cérébral, voriconazole, leucémie.

Abstract:

A case of disseminated invasive aspergillosis (IA) with cerebral involvement is reported in a Tunisian 57-year-old patient suffering from acute lymphoblastic leukemia. Respiratory symptoms including hemoptysis appeared the fortieth day after initiation of an anti-leukemia treatment. Three days later, the patient developed seizures and left-sided hemiparesis together with an ictera. Chest X-ray, CT and MRI were evocative of disseminated IA with pulmonary, cerebral, maxillary sinus and likely hepatic involvement. Aspergillus niger was isolated from sputum in four occasions, and the antigenemia was positive. The patient was treated with amphotericin B, then with voriconazole and underwent a surgical drainage of his cerebral abcess. The outcome was favourable without any clinical relapse 2 years later and the patient has remained in haematological remission. But, the patient ultimately died of a leukemia relapse on December 10th, 2009.

Key words : Invasive aspergillosis, cerebral abscess, voriconazole, leukemia.

INTRODUCTION

Invasive aspergillosis (IA) has been considered as a significant threat to neutropenic patients mainly those undergoing anti-leukemia chemotherapy and those submitted to hematopeitic stem cell transplantation [1, 2]. The diagnosis of IA is often difficult because of the poor specificity of clinical and radiological symptoms and the low sensitivity of mycological tests whereas monitoring of antigenemia may be misinterpreted [2, 3]. Presumptive antifungal treatment is associated with a high rate of failure and the mortality rate often exceeds 50% [2, 3]. Cerebral aspergillosis is a well-described complication of IA; its prognosis is usually very poor [4].
We, herein, report a case of IA with cerebral involvement in a Tunisian patient suffering from leukemia and treated with the combination of voriconazole and surgical drainage.

CASE REPORT

A 57-year-old Tunisian male patient was admitted to the department of Haematology at Farhat Hached teaching hospital in Sousse, Tunisia on April 4th, 2007 for a pre-B-acute lymphoblastic leukemia with fever. On admission, the neutrophil count was 357/mm3. The BFM 95 and inhibitors of tyrosin kinase induction chemotherapy protocol was started on April 17th together with ceftazidime and ofloxacine. On 40th day of hospitalization, the patient was febrile at 38°C and developed cough and hemoptysis. The chest X ray showed a poorly demarcated opacity of the upper lobe of the right lung. The thoracic computed tomography (CT) revealed an excavated lesion of the upper right lobe and the sinuses CT indicated a consolidation of the left maxillary sinus. Direct mycological examination of a single broncho-alveolar lavage (BAL) and of 10 sputum specimens was negative. *Aspergillus* niger was isolated in 4 sputum samples. Three days after the respiratory symptoms had appeared, the patient developed generalized seizures with a left-sided hemiparesis and ictera. Cerebrospinal fluid (CSF) cytochemical parameters proved to be normal. Cerebral CT showed an hypodense lesion of the right frontal area considered evocative of an ischemic cerebral infarction.
The biological assessment showed an hepatic cytolysis. Abdominal CT showed no abnormalities. Galactomannan antigenemia monitoring by the Platelia *Aspergillus*® ELISA kit (Bio-Rad, Marnes-la Coquette, France) was positive on three occasions. No galactomannane antigen was detected in CSF. Altogether, these findings were suggestive of a pulmonary IA with a probable sinusian, cerebral and hepatic involvement. The patient was initially treated with intravenous (IV) 1mg/Kg/day amphotericin B, which was discontinued on 10th day because of renal toxicity; and subsequently replaced with IV 200 mg x 2/day voriconazole for 14 days and then oral voriconazole at the same dosage. Fever and ictera disappeared by 7th day and the respiratory symptoms by one month. However, the patient kept presenting seizures once to twice/week. The cerebral CT performed on 15th day post-treatment showed the same findings as the first one. Magnetic resonance imaging (MRI) however, concluded to a cerebral abscess with pachymeningitis (Figure 1). A surgical drainage of the abscess was performed in July. The mycological examination of the drained fluid showed abundant dichotomous branching hyphae of 3-4 μm diameter very suggestive of *Aspergillus* (Figure 2). However, culture was negative. The patient was kept on oral voriconazole.

His clinical status gradually improved and he stopped developing seizures although the paresis of the left upper limb persisted.

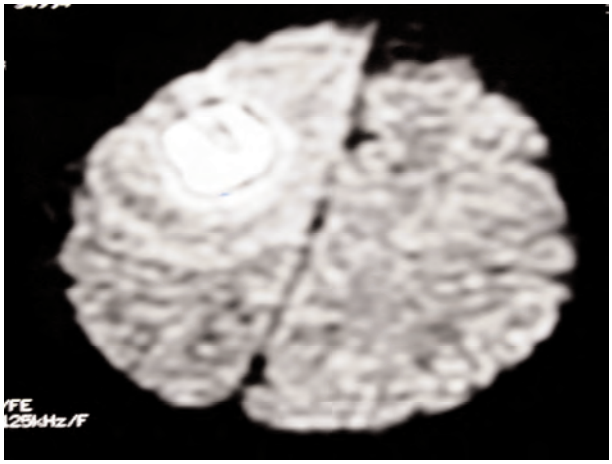

Figure 1 : Cerebral MRI. Cerebral abscess of the right frontal lobe
Figure 1 : IRM cérébrale. Abcés cérébral du lobe frontal droit

Figure 2 : *Aspergillus hyphae* in fluid drainage of the cerebral abscess (Gomori-Grocott's stain x 400).
Figure 2 : Filament aspergillaire dans le pus de drainage de l'abcés cérébral.(Coloration Gomori-Grocott x 400).

CT controls performed 4 months and 11 months later showed a marked regression of the cerebral abscess followed by the development of a sequellari lesion together with the persistence of the lung opacity. Antigenemia was monitored weekly during the first month following the neuro-surgical drainage and then, monthly for the next 15 months and found positive on two successive specimens obtained on January 2008 without any clinical symptoms. Since then, the patient has remained stable without any additional clinical or neurological impairment; and the follow up at 2 years didn't show any recurrence or new clinical symptoms. But, the patient ultimately died of a leukemia relapse on December 10th, 2009.

DISCUSSION

We, herein, report a case of disseminated IA with cerebral involvement in a Tunisian adult patient suffering from acute leukemia. IA is one of the most prevalent opportunistic infection in leukemia patients and those submitted to conditioning for hematopeitic stem cell transplantation [1, 2]. IA mainly affects the lungs. The disseminated forms as defined

by the involvement of at least two additional localizations are much less frequent [1, 3, 4]. In our patient, in addition to the highly probable cerebral aspergillosis, pulmonary, hepatic and sinusoidal invasiveness are very likely. The diagnosis of IA is often difficult and in most cases, only presumptive because the clinical symptoms are not specific and develop relatively late in the course of the disease [2, 3]. In our patient, the neurological symptoms appeared only a few days after the respiratory disorders, while the patient was in the late neutropenic phase.

Mycological examination is of limited value in IA, especially early in the infection. As far as specificity of mycological tests is considered, demonstration of *Aspergillus* in respiratory specimens needs to be interpreted with caution because positive results may be due to contamination of cultures by the laboratory environment or colonization of the respiratory tract by Aspergilllus spores without invasiveness. However, it has been shown that colonization is highly predictive of IA in severely neutropenic patients [5]. The definite diagnosis of IA requires demonstration of *Aspergillus hyphae* in tissues by histological analysis. However, biopsy is often not feasible. In our patient, the diagnosis of cerebral aspergillosis was performed only after surgery by the demonstration of very abundant *Aspergillus hyphae* in the cerebral abscess drained fluid. However, culture of brain material remained negative. The latter finding is in agreement with previous data on the very low sensitivity of culture of tissue specimens wether they are taken in pre or post-mortem [6]. This phenomenon remains unexplained. Additional mycological findings in our patient include isolation of *A. niger* in sputum on four occasions. Thus, the responsibility of this *Aspergillus* species in the IA diagnosed in our patient is very likely. According to most previous reports, *A. fumigates* and to a lesser extent *A. flavus* are the most frequently involved species in IA. *A. niger* is rather rare [2].

ELISA monitoring of soluble *Aspergillus* galactomannan is very useful in diagnosing IA and is admitted as a diagnostic criteria [7]. Its overall sensitivity is satisfactory and may be improved by the sequential repetition of the test [2, 3, 7]. However, false positive results caused by galactomannan containing food or drugs are not uncommon [8]. In addition, previous reported data argue for the usefulness of antigenemia in assessing the follow-up of patients undergoing antifungal therapy. In this respect, a decrease in the galactomannan amount is considered to be very suggestive of a favorable outcome whereas the persistence or the reappearance of the antigen may reflect a failure of treatment or a relapse of the disease [9]. Our patient was not checked for *Aspergillus* galactomannan before the development of clinical signs. Antigenemia was detected on three additional serum samples. In the specimens investigated all along the follow-up period, no antigenemia was detected except in two samples obtained on two successive days, five months following the surgical drainage of the cerebral abscess. As the clinical status of the patient kept improving and no resurgence or occurrence of additional symptoms could be demonstrated at that date, we cannot conclude on the significance of this finding, even though the contribution of persistent hyphae in the lung cannot be excluded.

Standard chest X-ray is an essential tool in monitoring patients at risk of IA despite its low sensitivity. Thoracic CT is more sensitive [2, 3]. In our patient, CT demonstrated an excavated lesion of the upper right lobe, which is a common finding in IA. Cerebral involvement occurs in 10 to 50% of IA cases [3, 4]. It is either secondary to an hematogenous dissemination from the lung lesions or from the adjacent sinus *Aspergillus* foci. MRI is the most contributive technique in diagnosing cerebral aspergillosis as CT finding may be misleading. In our patient, CT was misinterpreted; MRI findings were much more evocative of cerebral abscess. CT is of great contribution in detecting sinus involvement which is known to occur in 5 to 10% of IA cases [10]. In our patient, the maxillary sinus opacification revealed by CT was suggestive of an *Aspergillus* origin but no specimen was obtained for mycological examination. Even though the ictera seen in our patient was transient and rapidly resolved after treatment, the likeliness of hepatic dissemination cannot be discarded. Hepatic involvement seems to be rare and often proved at post-mortem [11]. The prognosis of disseminated IA and of cerebral aspergillosis is poor with a high mortality rate. It can, however, be improved by the early administration of antifungal therapy. Despite its high cost, voriconazole is proposed as the first line drug in IA because of its superiority in terms of effectiveness and tolerance as compared to amphotericin B. But, as stated by many previous reports on cerebral IA, voriconazole alone is poorly effective and drainage of lesions is needed [2, 3]. In our patient, surgical drainage of the cerebral abscess was of great contribution to the favorable short-term outcome. However, the relapse of the leukemia remains an element of a poor prognosis associated with a very high mortality.

CONCLUSION

The herein reported case suggests that cerebral involvement may not be uncommon in IA of the leucemic patient and should be suspected whenever neurological symptoms occur. On the other hand, our findings argue for the usefulness of the combination of voriconazole and surgical drainage in order to achieve a therapeutic success and to improve the prognosis.

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