Prostatic and renal aspergillosis due to \textit{Aspergillus fumigatus} in a patient receiving alemtuzumab for chronic lymphocytic leukaemia

\textit{Infection fongique prostatique et rénale à Aspergillus fumigatus chez un patient traité par alemtuzumab pour une leucémie lymphoïde chronique}

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**KEYWORDS**

Leukaemia; \textit{Aspergillus fumigatus}; Alemtuzumab; Prostate; Kidney

**Summary**

\textbf{Objective.} — Treatment of chronic lymphocytic leukaemia (CLL) is rapidly evolving, with emerging new drugs. Alemtuzumab is a monoclonal antibody recognizing CD52 antigen approved in the treatment of relapsing-refractory CLL. A frequent side effect is the immunosuppression and patients treated with alemtuzumab risk to develop fungal infections such as aspergillosis.

\textbf{Patient and methods.} — This case report is about a patient who developed an uncommon localization of aspergillosis: prostatic and renal, after a treatment by alemtuzumab mono-therapy. During the week 8 of alemtuzumab, the patient presented fever, urinary frequency and urologic symptoms. Persistence of fever with common antibiotic therapy led to realize a tomography that showed prostatic and renal abscess (70 mm and 29 mm). It was decided to realize a prostatic biopsy.

\textbf{Results.} — Histological findings showed suppurative abscess with ischemic necrosis and fungal proliferation, with branched fungal hyphae. Direct examination was negative. Culture on Sabouraud’s agar revealed a mould identified as \textit{Aspergillus fumigatus}. The organism was
susceptible to voriconazole (MIC: voriconazole 0.25μg/mL).

Conclusion. — Because of the main side effect of alemtuzumab is immunosuppression, we have to research fungal infections such as Aspergillosis, particularly in patients with fever resistant to common antibiotic therapy.

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Introduction

Treatment of chronic lymphocytic leukaemia (CLL) is rapidly evolving, with emerging new drugs and new therapeutic associations. Alemtuzumab is a monoclonal antibody recognizing CD52 antigen, whose action is mainly mediated by ADCC (Antibody Dependant Cell Mediated Cytotoxicity) but also by complement activation and induction of apoptosis. Alemtuzumab is approved in the treatment of relapsing—refractory CLL [2]. A frequent side effect is immunosuppression, and the risk to develop fungal infections such as Aspergillosis [12]. We report the first case, to our knowledge, of a prostatic aspergillosis after a treatment by alemtuzumab. Usually, pulmonary aspergillosis is the most common complication.

Case report

We report the case of a 68-year-old man who received for a chronic lymphocytic leukaemia a first line R-FC therapy (rituximab fludarabine and cyclophosphamide) for three cures and in a second line R-Chop (rituximab cyclophosphamide doxorubicine and prednisone) for two cures. But the disease increased and the patient received a new line treatment by alemtuzumab monotherapy. This agent is usually given with antifungal and antiviral prophylaxis to prevent pneumocystosis [10]. The patient received prophylactic treatment with trimethoprim/sulfamethoxazole three times a week and valaciclovir 500 mg twice a day but no antifungal agent. The patient presented during the week 8 of alemtuzumab therapy, fever, urinary frequency and painful burning sensations. He had a past medical history of hypertension, hypercholesterolemia, appendectomy and meniscectomy.

He received a first line of antibiotics by fluoroquinolone (ciprofloxacine: 500 mg twice a day). Cytobacteriological examination of the urine shows leucocyturia but no germs at bacteriological examination. Renal echography described a renal right abscess measuring 29 mm. The persistence of fever and urologic symptoms led to realize a cerebral, sinus, thoracic and abdominal and pelvic computed tomography (CT). It showed a prostatic abscess measuring 70 mm (Fig. 1), and a right renal abscess measuring 29 mm (Fig. 2). No abnormality was described at cerebral, sinus and thoracic CT. It was decided to start intravenous antibiotic therapy with ceftazidime and amikacine. The general aggravation led to realize a prostatic biopsy 7 days later. Histological examination pointed out a suppurative abscess with ischemic necrosis and fungal proliferation, with septate branched hyphae. Culture on Sabouraud’s agar grew A. fumigatus, susceptible...
to voriconazole and amphotericin B and resistant to itraconazole. The Minimum Inhibitory Concentration (MIC) were 0.25 mg/mL, 0.5 mg/mL and 32 mg/mL respectively. The MIC were performed with the E-Test according to the manufacturer’s instructions (AB Biodisk, Sweden). Aspergillus galactomannan antigenemia assay (Pastorex Aspergillus kit Bio-Rad, Marne-la-Coquette, France) realized before, during and after diagnosis was always negative.

We started intra-venous voriconazole during 7 days, then oral voriconazole (200 mg twice a day). In uncommon single organ infections, voriconazole is recommended in first line therapy (IDSA: Infectious Diseases Society of America). Really, based on the strength of the randomized study comparing voriconazole to D-AMB [16], the IDSA recommends voriconazole for primary treatment of these uncommon manifestations of invasive aspergilliosis (B-III). The plasmatic through level of voriconazole was 2.55 mg/l (threshold efficiency = 1 mg/L). The clinician decided to increase the posology (300 mg twice a day) one month later because of the residual rate was inadequate.

A CT control was performed once a month and showed progressive regression of the abscesses.

After 8 months of treatment, voriconazole was discontinued because of the complete regression of the abscesses.

Discussion

Infectious complications continue to be a major cause of morbidity and mortality in patients with CLL. Review of the literature revealed only few cases of prostatic aspergillosis in immunodeficient patients [7]. Recognized aspergillosis risk factors include a history of immunosuppression, malignancy, organ transplantation, long term corticosteroid use, drug abuse and trauma. Because of the mortality rate of this disease approaches or exceeds 50% in high-risk patient groups, the prevention became an issue of major importance in the management of all high-risk patients. Various strategies have been adopted to reduce the burden of this disease. The main approaches involved a reduced exposure of high-risk patients to Aspergillus spores, through environmental control measures. It has been shown that HEPA (High Efficiency Particulate Air) filtration can reduce or even eliminate Aspergillus spores from the air [3,4,14,15]. To our knowledge, this is the first report in the literature of prostatic aspergillosis after alemtuzumab treatment. The cases found in the literature report ophthalmologic, osteomyelitis and pulmonary aspergillosis with patients treated with alemtuzumab [1,8]. Voriconazole is the first line treatment for this pathology.

By rapidly depleting lymphocytes and monocytes but not affecting neutrophils and hematopoietic stem cells, monoclonal antibodies such as rituximab and alemtuzumab, have introduced a new spectrum of infectious complications. It is caused by pathogens such as Pneumocystis, Listeria, Mycobacteria, Herpesviruses Candida and Aspergillus, related to the cellular immune suppression induced by these agents [5,6,9,11,13].

Conclusion

Infections have been known to have a major impact on the course of patients with CLL over many decades. Because of the main side effect of alemtuzumab is immunosuppression, we have to research and prevent fungal infections such as aspergillosis, particularly in patients with fever resistant to common antibiotic therapy.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


Figure 2 Abdominal-pelvic tomography with injection of contrast. Pointer shows renal right abcess (29 mm) due to Aspergillus fumigatus. Scanner abdomin pelvien avec injection. la flèche montre un abcès prostatique (70 mm) à Aspergillus fumigatus.


