

# Cerebral aspergillosis in immunocompromised patient successfully treated with voriconazole

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## Abstract

Cerebral aspergillosis is a severe invasive mycosis occurring in immunocompromised patients. This pathology is associated with a high rate of mortality and is a current complication of pulmonary invasive aspergillosis.

We report the case of a 44-year-old immunocompromised male with a recent history of oropharyngeal carcinoma. At his admission the patient presented with fever and confusion. Imaging revealed the presence of a cerebral abscess combined with lung infiltrates. During hospitalization and despite a broad-spectrum antibiotic regimen his condition worsened. A thin needle aspiration of the abscess was performed for diagnosis purpose. Histological examination of the tissue showed septate and branched hyphae with 45° angles suggestive of *Aspergillus*. A real-time PCR specific for the detection of *Aspergillus* sp. was carried out and confirmed the fungal etiology of the abscess. Rare colonies of *A. fumigatus* were isolated a few days later. The diagnosis of invasive pulmonary aspergillosis complicated by a cerebral dissemination was confirmed. Antifungal treatment based on voriconazole 4 mg/kg q12h was introduced and the dosage was successfully increased up to 5 mg/kg q12h by drug monitoring.

This case highlights the usefulness of the *Aspergillus* PCR for the rapid identification of hyphae in tissue biopsies (or in the event of negative culture), and the importance of therapeutic drug monitoring in treatment by voriconazole.

## Background

The most common clinical form of cerebral aspergillosis is a brain abscess. The fungus spreads either from an adjacent sinus lesion or via hematogenous pathways from a pulmonary infection. The central nervous system is the most common site of dissemination.

Cerebral aspergillosis complicates between 10 to 20% of pulmonary infections. The territories of the anterior and middle cerebral arteries are most often affected. *Aspergillus fumigatus* is the most frequently implicated because it is the most virulent.

The symptoms are nonspecific and present as neurological deficits, an altered state of consciousness, seizures, or symptoms of intracranial hypertension. Fever is present in 60% of patients.

Risk factors of cerebral aspergillosis are the same as those of invasive pulmonary aspergillosis: hematologic cancers, marrow or stem cell transplants, chemotherapy, solid organ transplants, autoimmune disease, AIDS, long-term corticosteroid treatment, diabetes.

*Aspergillus* tends to invade the walls of blood vessels. As consequence, brain abscesses associated with infarctions and secondary hemorrhages can occur.

## Objectives

To highlight the usefulness of *Aspergillus* PCR for the rapid identification of hyphae in tissue biopsies or in case of negative culture.

To point out the importance of drug monitoring in treatment by voriconazole.

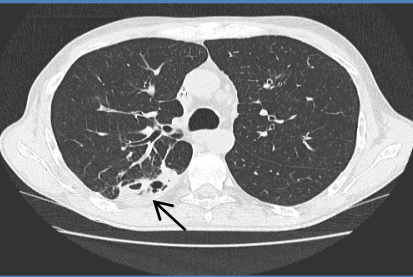


Figure 1. Thoracic CT showing right basal condensation with cavitations.

## History

**Admission.** A 44-year-old patient was admitted to the University Hospital of Liège March 1, 2012 for diagnostic biopsy of a cerebral abscess. The patient had previously been admitted to a peripheral hospital for febrile alteration of the general condition following chemo-radiotherapy treatment for oropharyngeal cancer. Despite broad-spectrum antibiotic therapy, the patient's condition deteriorated.

**Physical examination** revealed confusion, hypoventilation at lung bases, left upper limb paresis and impairment of the left field of vision.

**Biology.** WBC and neutrophil counts were respectively: 2500 and 1960 /mm<sup>3</sup>. The CRP was 336 mg/L. LCR examination showed RBC at 100/mm<sup>3</sup>, WBC at 747/mm<sup>3</sup> (with 81% neutrophil), hyperproteinorrhachia (750 mg/L) and hypoglycorrhachia (0.25 mg/L).

**Microbial culture.** *Escherichia coli* and *Pseudomonas aeruginosa* were isolated from blood culture. *Serratia marcescens* was found in sputum. LCR culture was negative.

**Imaging examination.** Thoracic CT showed bilateral pulmonary disease probably infectious, manifested by condensations partially cavitating at the sloping portion of both lungs, as well as multiple nodular necrotic or cavitating elements scattered in both pulmonary fields (Figure 1). The MRI showed an abscessed collection, 35 cm in diameter, fronto-parieto-temporal right at the level of the corona radiata, extending partially to the right lateral ventricle and around which a wide reactive, edematous area was found (Figure 2).

**Treatment at admission.** The antibiotic therapy was meropenem, vancomycin, amikacin and ciprofloxacin.

## Results of investigations

**Thin needle aspiration** of the abscess was performed for diagnostic purpose.

**Anatomopathology.** Histological examination of the hematoxylin stained tissue showed septate and branched hyphae with 45° angles suggestive of *Aspergillus* (figure 3).

**Microbial diagnosis.** A real-time PCR targeting the 18S rRNA fungal genes and specific for the detection of *Aspergillus* sp. was carried out on the biopsy tissue (ref Kami et al.). The amplification of nucleic acids specific of *Aspergillus* sp. confirmed the fungal etiology of the abscess. A few days later, rare colonies of *A. fumigatus* were isolated Sabouraud agar medium. The in-vitro susceptibility testing was carried out by E-test (at the national reference center for invasive mycosis, KUL) and MIC's were as follows: 0.5 µg/ml for voriconazole, 1 µg/ml for itraconazole and 0.25 µg/ml for posaconazole. Galactomannan detection (Platelia™ *Aspergillus* Ag kit, Bio-Rad laboratories, USA) on serum was negative (index at 0.13). Blood cultures were all negatives. No respiratory sample was tested.

**Diagnosis.** The diagnosis of invasive pulmonary aspergillosis (based on thoracic CT images) complicated by a cerebral dissemination was confirmed.

**Treatment** was based on the use of oral voriconazole 6 mg/kg q12h on the first day followed by 4mg/kg q12h. At this posology, a concentration of 3.3 mg/ml (normal values: 2.0-6.0 mg / ml) was detected and the dosage was considered appropriate.

**Evolution.** A week later, a cerebral CT showed a decrease in volume of the abscess and a re-expansion of the right ventricular system. A thoracic CT revealed a partial regression of bi-basal condensations, together with most of the nodular lesions previously visible. The inflammatory syndrome was also declining. After 3 months of treatment, the patient noticed a decrease in his visual field during reading and driving his car. The cerebral CT, performed in emergency, confirmed the appearance of new abscessed lesions on the temporal internal ipsilateral level. Voriconazole was dosed at 2.7 mg / ml and the dosage was increased to 5 mg / kg q12h leading to a complete clinical resolution of symptomatology and a radiological improvement of lesions.

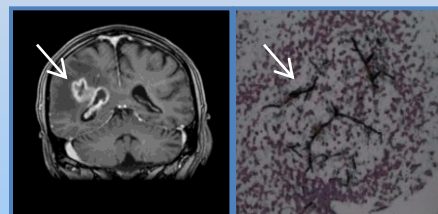


Figure 2. Cerebral MRI. Fronto-parieto-temporal right abscessed collection extending to the right lateral ventricle. It is surrounded which a wide edematous area.

Figure 3. Gomori-Grocott stain (50X magnification) showing large, regular, branched hyphae suggestive of *Aspergillus*.

## Discussion

The diagnostic approach of branched hyphae seen on histological examination consists in combining cultures with PCR specific to *Aspergillus*. PCR gives a result within a few hours and allows a rapid diagnosis if the culture is negative and also a rapid specific treatment. In this clinical case, it was performed on biopsy material, but studies also demonstrate its effectiveness when performed on the CSF. However, this PCR cannot be used to identify the species of *Aspergillus*. For this purpose, molecular sequencing of ITS genes should be carried out. This was not performed in this case because the identification was performed by culture.

Testing for the galactomannan antigen is a rapid technique that can also guide the diagnosis. The test is validated for serum and BAL. It is especially noticeable in patients with hematological cancers or who have received hematopoietic cell transplant. The detection of the galactomannan antigen is possible on CSF samples but the test is not yet standardized by the manufacturer. It was unfortunately not performed for this patient.

The rapid establishment of an effective treatment is of paramount importance, since cerebral aspergillosis is associated with a high mortality rate, ranging from 88 to 99% depending on the series. The treatment of cerebral aspergillosis recommended by the Infectious Disease Society of America consists of voriconazole 6 mg/kg/12 hours on the first day followed by 4 mg/kg/12 hours. Indeed, voriconazole is considered as the treatment of choice due to its very good penetration into the central nervous system (CSF rate estimated at 50% saturation). This case emphasizes the importance of voriconazole dosage. The blood rate must be kept high enough to ensure an optimal concentration in the CSF and the cerebral parenchyma.

## References

- Makus Ruhnke et al. CNS Aspergillosis: Recognition, Diagnosis and management. CNS Drugs 2007; 21(8): 659-676.
- T. Nadkarni, A. Goel. Aspergillosis of the brain: an overview. J Postgrad Med 2005 Vol 51 Suppl 1; 537-541.
- Masahiro Kami et al. Use of Real-Time PCR on Blood Sample for Diagnosis of Invasive Aspergillosis. Clinical Infectious Disease 2001; 33; 1504-12

## Conclusion

Real-time PCR realized on tissue biopsy is very useful to diagnose cerebral aspergillosis but cannot identify the species of *Aspergillus*. For this purpose, molecular sequencing must be carried out. Voriconazole dosage is essential to adapt the voriconazole posology. Indeed, the blood rate must be kept high enough to ensure an optimal concentration in the cerebral tissue and avoid treatment failure.