

MULTIPLE CEREBRAL CRYPTOCOCCOMAS IN AN IMMUNOCOMPETENT PATIENT TREATED WITH VORICONAZOLE

MULTIPLES CRYPTOCOCCOMES CEREBRAUX TRAITES PAR VORICONAZOLE CHEZ UN PATIENT IMMUNOCOMPETENT

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Abstract

Cryptococcosis is extremely rare in immunocompetent hosts. Cerebral cryptococcomas are difficult to treat and require prolonged antifungal therapy. We report the case of a healthy 46-year-old man who developed a prolonged fever and cough. Radiology has suspected a tumor process of the lung. Diagnosis of pulmonary cryptococcosis was confirmed after lung lobectomy. The patient was treated with amphotericin B switched by fluconazole. Four months later, he developed seizures. Cerebral MRI showed multiple cerebral enhancing lesions. The diagnosis of cerebral cryptococcoma was established by brain stereotactic biopsy. The patient was treated with amphotericin B and fluconazole switched by flucytosine and voriconazole for a total therapy of 2 years. The clinical outcome was good without signs of relapse.

This case shows that cryptococcosis can occur in immunocompetent host and can be successfully treated with voriconazole

Key words : Cerebral cryptococcoma; immunocompetent; antifungal treatment; voriconazole

Résumé

La cryptococcose est rare chez le sujet immunocompétent. La cryptococcose cérébrale est difficile à traiter et nécessite un traitement anti fongique prolongé. Nous rapportons le cas d'un patient âgé de 46 ans, sans antécédents, hospitalisé pour une toux et une fièvre prolongée. Le scanner thoracique a montré une masse pseudo tumorale pulmonaire correspondant à une cryptococcose pulmonaire après lobectomie. Il a été traité par amphotéricine B puis par fluconazole. Quatre mois plus tard, il a développé des crises convulsives. L'IRM cérébrale a montré des lésions annulaires. Le diagnostic de cryptococcose cérébrale a été confirmé par une biopsie stéréotaxique cérébrale. Le patient a été traité par amphotéricine B et fluconazole puis par flucytosine et voriconazole pour une durée totale de 2 ans. Il est guéri sans rechute. Nous démontrons la possibilité de survenue de la cryptococcose sans immunodépression sous jacente. Le voriconazole constitue une alternative thérapeutique intéressante.

Mots clés : Cryptococcome cérébral; immunocompétent; traitement anti fongique; voriconazole

ملخص

المستخفيات أمر نادر الحدوث في المرضى الذين يعانون من نقص المناعة. المستخفيات الدماغية يصعب علاجها وتتطلب فترة طويلة للعلاج ضد الفطريات. نقدم تقريرا عن حالة مريض يبلغ من العمر 46 عاما وليس له سوابق مرضية و الذي وقع إيوؤه في المستشفى لوجود سعال وحمى لفترة طويلة. أظهر الصدر بواسطة التصوير الطبي بالأشعة المقطعية وجود كتلة لشبه ورم مطابقة لتورمات المستخفيات الرئوية بعد استئصال الفص. تم العلاج بواسطة الأمفوتريسين ب وفلوكونازول. بعد أربعة أشهر ظهرت نوبات صرع لدى المريض.

أظهر كشف الدماغ بالرنين المغناطيسي آفات حلقيه. تم تأكيد تشخيص المستخفيات الدماغية عن طريق اخذ خزعة الجسم الدماغية. وعولج المريض مع الأمفوتريسين ب و فلوكونازول و فاريكونازول و فلوستيزين لمدة سنتين. و قد تم حينها الشفاء هو دون الانتكاس. علينا أن نبرهن على إمكانية حدوث المستخفيات دون وجود الكابحة المناعية كسابقة مرضية. و يعتبر دواء فاريكونازول هو البديل العلاجي المهم.

الكلمات المفاتيح : المستخفيات الدماغية ; الكابحة المناعية ; العلاج المضاد للفطريات ; فاريكونازول

Cryptococcosis is extremely rare in immunocompetent hosts [1,2]. We report a case of multiple cerebral cryptococcoma occurring in an immunocompetent man which was successfully treated with voriconazole.

A previously healthy 46-year-old joiner was admitted, in our department, with a 2-weeks history of fever, cough and headache. The chest X-ray and the computed tomography scan, showed a large tumor-like opacity in the left upper lung lobe. Brain scan was normal. Lumbar puncture wasn't performed because there wasn't signs of meningitis and headache regressed spontaneously. We suspected the diagnosis of lung carcinoma. He underwent an upper left lobectomy. Pulmonary cryptococcosis was confirmed by mycological and anatomopathological examination of the tumor. The human immunodeficiency virus (HIV) serology was negative. The CD4+T lymphocyte count was normal and there was no other causes of immunosuppression. The patient was treated with amphotericin B (1 mg/kg/day) for two weeks followed by fluconazole (400 mg/day) for two weeks.

Four months later, he was hospitalized for headache, vomiting, generalised seizures, and left facial nerve paralysis. Brain MRI showed multiple enhancing lesions in the right and the left insula and in the left cerebellar hemisphere, with a surrounding edema (Figure 1). On the brain stereotactic biopsy, Indian ink preparation showed typical encapsulated fungal bodies, and the cryptococcal antigen was positive. Moreover, the cryptococcal antigen was positive in urine. The diagnosis of cerebral cryptococcoma was established. The patient was treated with amphotericin B (1 mg/kg/day) and fluconazole (400 mg/day). Six months later, the cerebral lesions remained unchanged, and the patient developed renal failure due to amphotericin B. Treatment was switched by oral voriconazole (200 mg twice daily) and flucytosine (100 mg/kg/day), which had been maintained for 18 months. The clinical outcome was good. The tolerance of treatment was excellent. Twenty four months after stopping the antifungal therapy, an MRI was performed and showed a significant regression of the size and number of cerebral lesions. Until 2016, the patient is fine without signs of relapse.

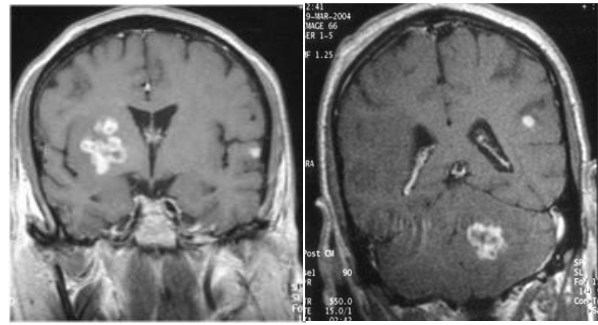


Fig 1 a

Fig 1 b

Figure 1 : Brain MRI (T-1 weighted with gadolinium injection)

(a) multiple enhancing coalescent lesions in the right insula with a surrounding oedema

(b) enhancing lesions in the left insula and in the left cerebellar hemisphere

DISCUSSION

We report a new case of cryptococcosis in an immunocompetent patient. Although it has never been conclusively documented, cases of cryptococcosis are thought to result to inhalation of airborne fungi from an environmental source. The exposure to *Cryptococcus (C). neoformans* is particularly common in certain groups such as pigeon breeders and laboratory workers. For our patient, the infection was probably acquired via inhalation of airborne fungi when handling wood. Exposure to eucalyptus, fir, maple, alder, cedar, spruce and pine trees, the ecological niche of *C. gattii*, and smoking were identified as risk factors [3, 4, 5, 6].

Both *C. neoformans* and *C. gattii* have a propensity to cause pulmonary and central nervous system diseases [6]. Simultaneous lung and central nervous system infections are common (52%) [5], and may be mistaken for malignancy or bacterial abscesses [6]. Otherwise, as described in previous reports [1,2,7], in our case, we were unable to conclude whether the cerebral injury was consecutive to a haematogenous spread induced by the lung surgery or if it was concomitant to the first invasion of the lung by this micro-organism.

Cryptococcosis of the central nervous system usually present as meningitis, and on rare occasions as single or multiple focal masses called cryptococcomas that are more common in immunocompetent hosts [3, 8].

They can be seen in HIV infected patients during an immune reconstitution syndrome when receiving succeeding initiation of highly active antiretroviral therapy [9, 10].

In HIV-negative hosts, intracranial infection with *C. gattii* is associated with more neurological complications, delayed response to therapy, and higher incidence of neurosurgical intervention, in comparison to the disease due to *C. neoformans*, despite similar susceptibility of the 2 species to antifungal drugs [11].

Cerebral cryptococcomas are difficult to treat and require prolonged antifungal therapy [11]. Treatment is based on systemic antifungal therapy with surgical excision of accessible and large cryptococcomas (> 3 cm) [11, 12]. The treatment of choice is Amphotericin Bd combined with flucytosine for an induction therapy, followed by a consolidation therapy with fluconazole [11]. We report the successful treatment of multiple cerebral cryptococcomas-using antifungal therapy only with amphotericin B and fluconazole switched 2 weeks later, by voriconazole and flucytosine. Voriconazole appears to be at least 10 times more potent than fluconazole against clinical isolates of *C. neoformans* [13]. It is well tolerated and can be used for a long period especially if other molecules are unavailable or contraindicated. Sabbatani et al [14] have reported a case of cerebral cryptococcoma completely cured with surgery and voriconazole. For our patient, the treatment was maintained for two years given the severity of the disease and the lack of recommendations regarding the duration of antifungal therapy.

In conclusion, our case shows that patients with pulmonary cryptococcosis should be followed even if recovery seems to be complete given the risk of cerebral dissemination. Voriconazole seems to be a successful alternative treatment for cerebral cryptococcoma, however, specific recommendations for its use in this indication are needed.

REFERENCES

- [1] Kiertiburanakul S, Wirojtananugoon S, Prachartam R, Sungkanuparph S. Cryptococcosis in human immunodeficiency virus-negative patients. *Int J Infect Dis* 2006,10: 72-8.
- [2] Rozenbaum R, Goncalves AJR. Clinical epidemiological study of 171 cases of cryptococcosis. *Clin Infect Dis* 1994,18:369-80.
- [3] Mitchell DH, Sorrell TC, Allworth AM, Heath CH, Georger AR, Papanaooum K, et al. Cryptococcal disease of the CNS in immunocompetent hosts: Influence of cryptococcal variety on clinical manifestations and outcome. *Clin Infect Dis* 1995, 20:611-6.
- [4] Ellis DH, Pfeiffer TJ. Natural habitat of *Cryptococcus neoformans* var.*gattii*. *J Clin Microbiol* 1990,28:1642-4.
- [5] Sharon C-A Chen, Monica A.Salvin, ChristopherH.Heath, E.Geoffrey Playford, Karen Byth et al. Clinical Manifestations of *Cryptococcus gattii* infection: determinants of neurological sequelae and death. *Clin Infect Dis* 2012,55:789-98
- [6] Walraven CJ, Gerstein W, Hardison SE, Wormley F, Lockhart SR, Harris JR et al. Fatal Disseminated *Cryptococcus gattii* Infection in New Mexico .*PLoS One* 2011,6: e28625
- [7] Kerkering TM, Duma RJ, Shadomy S. The evolution of pulmonary cryptococcosis: clinical implications from a study of 41 patients with and without compromising host factors. *Ann Intern Med* 1981, 94:611-6.
- [8] SRai, RSK Marak, S Jain, TN Dhole. Posterior fossa midline cryptococcoma in a patient with idiopathic CD4 lymphocytopenia. *Indian J Med Microbiol* 2012, 30:367-70
- [9] Cattelan AM, Trevenzoli M, Sasset L, Lanzafame M, Marchioro U, Meneghetti F. Multiple cerebral cryptococcomas associated with immune reconstitution in HIV-1 infection. *AIDS* 2004,18:349-51.
- [10] Sitapati AM, Kao CL, Cachay ER, Masoumi H, Wallis RS, Mathews WC. Treatment of HIV-Related Inflammatory Cerebral Cryptococcoma with Adalimumab. *Clin Infect Dis* 2010, 50:e7-10
- [11] Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ et al. Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2010,50:291-322
- [12] Saag MS, Graybill RJ, Larsen RA, Pappas P, Perfect JR, Powderly WG, et al. Practice guidelines for the management of cryptococcal disease. *Clin Infect Dis* 2000; 30:710-8.
- [13] Sabo JA, Abdel-Rahman SM. Voriconazole: a new triazole antifungal. *Ann Pharmacother* 2000,34:1032-43.
- [14] Sabbatani S, Manfredi R, Pavoni M, Consales A, Chiodo F. Voriconazole proves effective in long-term treatment of a cerebral cryptococcoma in a chronic nephropathic HIV-negative patient, after fluconazole failure. *Mycopathologia* 2004,158:165-71.