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Case study Intracavitary amphotericin B in the treatment of intracranial aspergillosis

Cahit Kural^a, Mehmet Ilker Ozer^a, Mehmet Can Ezgu^{a,*}, Royal Mehtiyev^a, Soner Yasar^a, Ahmet Murat Kutlay^a, Mehmet Kadri Daneyemez^a, Onder Onguru^b, Ersin Erdogan^c, Yusuf Izci^a

^a University of Health Sciences, Gulhane Training and Research Hospital, Department of Neurosurgery, Ankara, Turkey ^b University of Health Sciences, Gulhane Training and Research Hospital, Department of Pathology, Ankara, Turkey ^c Ufuk University, Department of Neurosurgery, Ankara, Turkey

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ABSTRACT

Intracranial aspergillosis is a rare infectious disease of the central nervous system with high mortality rates. Our aim is to present 3 cases of intracranial aspergillosis who were surgically treated with intra-cavitary amphotericin B administration.

First case was a 21-year-old male patient. Allogeneic stem cell transplantation treatment was performed because of aplastic anemia and vocal cord paralysis developed 10 days after treatment. Multiple aspergillosis abscesses were observed in the cranial magnetic resonance imaging (MRI). Cerebral lesions were excised and 0.3 cc of amphotericin B was applied locally. Second case was a 18year-old male patient treated for acute lymphocytic leukemia. MRI was performed on the development of consciousness change during treatment and right frontal abscess was detected. The abscess was excised and amphotericin B was applied locally. Third case was a 45-year-old woman with mastectomy. She had chemotherapy after surgery and had blood stem cell transplantation because of pancytopenia. Two months after treatments, MRI was performed on the development of ataxia and a cerebellar abscess was detected. The abscess was surgically excised and local amphotericin B was applied.

The first case deceased 2 weeks after surgery and the second case died 2.5 years later due to multiorgan failure. The third case is stil alive and neurologically stable after 14 years of surgical treatment.

In intracranial aspergillosis, intracavitary amphotericin B therapy may be used as an adjunct after the surgical excision of abscess. This procedure may contributes to the regression of abscess or prevention of the recurrence. But comparative clinical studies are needed for more accurate conclusions.

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1. Background

Intracranial aspergillosis accounts for 5–10% of intracranial fungal infections [1,2,3,4]. It tends to appear in immunosuppressive patients. Systemic antifungal therapy, surgical excision and intracavitary amphotericin B administration are treatment options [2,3,4,5,6,7].

We reported three cases of intracranial aspergillosis treated with intracavitary amphotericin B and discussed this procedure in the context of current literature. Informed consent was obtained from all individual participants included in the study.

* Corresponding author. E-mail address: mehmetcan.ezgu@sbu.edu.tr (M.C. Ezgu).

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2. Clinical presentation

Case 1: This is a 21-year-old male patient. He previously underwent allogeneic stem cell transplantation for aplastic anemia. One week later, vocal cord paralysis and swallowing difficulty were developed. Cranial MRI showed multiple lesions in the brain stem, bilateral occipital and right frontal lobes (Figs. 1a, 1b, 1c, 2). The patient was operated 21 days after the transplantation, and abscesses in the brain stem and occipital lobes were totally removed. The intraoperative abscess sample was reported as aspergillus. Therefore, 0.3 cc of amphotericin B was administered locally in the abscess cavity in occipital lobe. Histopathological examination showed large areas of necrosis. Focal collections of polymorphonuclear leukocytes were present in necrosis. Multinuclear giant cells and fibrosis were observed in the surrounding parenchyma. Macrophages were also seen in parenchymal zone close

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Fig. 1a. Intraoperative view of the abscess at brainstem.

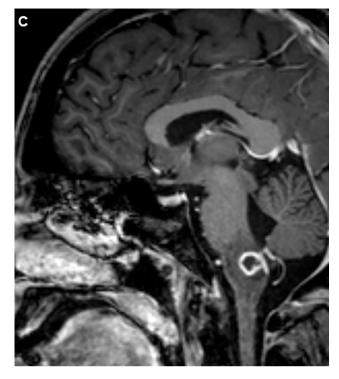


Fig. 1c. Sagittal view of the abscess on T1-weighted post-contrast MRI.

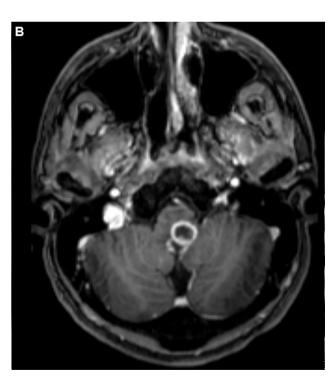


Fig. 1b. Axial view of the abscess on T1-weighted post-contrast MRI.

to necrosis. Inside the necrotic areas, abundant fungal organisms proliferating in the walls and lumens of vascular structures were observed. Methenamine silverstain revealed that fungal organisms form uniform, slender, acutely branching, septate hyphae (Fig. 3a, Fig. 3b). Intravenous amphotericin B was administered during the postoperative period. Neurological examination of the patient

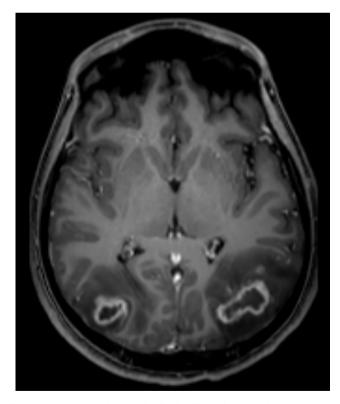


Fig. 2. Contrast enhanced lesions localized at bilateral occipital lobe. Lesions were hypointense in T1-weighted series and showed peripheral linear enhancement in post-contrast series.

was normal after surgery. But respiratory distress showed up at the 7th day after the operation, and the patient died due to multiorgan failure.

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C. Kural et al./Journal of Clinical Neuroscience xxx (2018) xxx-xxx

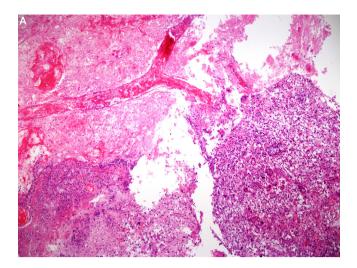


Fig. 3a. Large area of necrosis with focal inflammatory in filtrate containing polymorphonuclear leukocytes and macrophages in surrounding parenchyma (Hematoxylin-Eosin, $\times 100$).

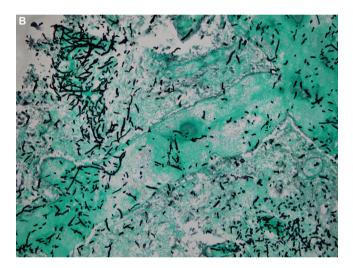


Fig. 3b. Uniform, slender, acutely branching fungal hyphae consistent with Aspergillus in necrosis around vessels (Gomori's Methenamine silver stain, \times 200).

Case 2: This is a 18-year-old male patient with a history of acute lymphocytic leukemia. Antibiotherapy was performed because of febrile neutropenia developed in the follow-up period. During the third week of treatment, clouding of consciousness and tendency toward sleepiness were developed. On MRI, there was a lesion at the right frontal lobe, approximately 55x60 mm in size with a peripheral edema and peripheral contrast enhancement (Fig. 4a). Lesion was surgically excised (Fig. 4b). Following the surgical excision of the abscess, amphotericin B was administered locally in the surgical cavity. Antifungal treatment continued after surgery. Patient was completely improved within 2 months. Histopathological examination revealed the diagnosis of cerebral aspergillus. Postoperative 6-month MRI revealed that the lesion completely disappeared. Nonetheless the patient died 2.5 years later due to multiple organ failure.

Case 3 This is a 45 year-old female patient who underwent mastectomy for breast cancer and then received chemotherapy. Due to the development of pancytopenia, autologous blood stem cell transplantion have been performed. Two months after these treatments, the patient developed ataxia. Cerebellar lesion was seen on MRI (Fig. 5a). Cerebellar abscess was surgically removed.

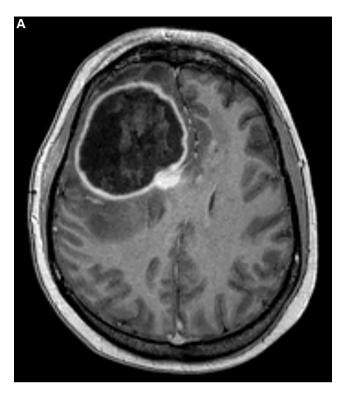


Fig. 4a. Right frontal lobe lesion approximately 55×60 mm in size with a peripheral edema and peripheral contrast enhancement.

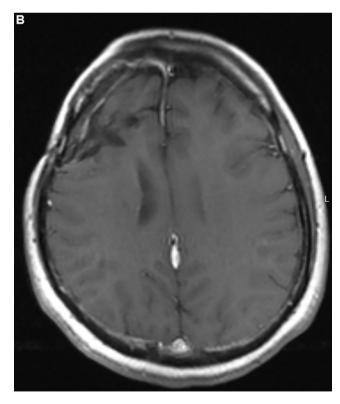


Fig. 4b. There is not any residual lesion after surgery.

Histopathological examination revealed the presence of aspergillus. Postoperative neurological examination was normal. At the 5th postoperative week, MRI was repeated on the resumption of the ataxia in the patient. Reappearance of the abscess was

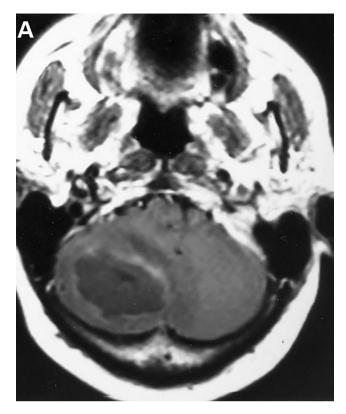


Fig. 5a. Cerebellar abscess lesion in post-contrast MRI (4) (From Neurosurgery, with permission).

observed in the region corresponding to the first surgical site. Abscess was excised again and local amphotericin B was applied. The patient received Amphotericin B for 3 months. There was no abscess formation at postoperative 3rd month MRI (Fig. 5b). All complaints were completely resolved after 3 months from operation. This case was already published by the authors [4]. Today, the patient is still alive after 14 years of cerebellar abscess excision.

3. Discussion

In the literature, it has been shown that invasive aspergillosis usually develops in malignant tumors and in chronic immunosuppressive patients [2,8]. Risk factors for cranial aspergillosis include long-term and severe neutropenia, long-term high-dose steroid therapy, acquired immunodeficiency syndrome (AIDS), and bone marrow transplantation [3,4]. In these cases, mortality rates range from 90% to 100% [1,9].

These high levels of mortality are not solely related to cerebral involvement. Most cases are immunosuppressive and patients with opportunistic infections are known to have died [5,10]. Cranial aspergillosis can occur with clinical signs such as convulsions, fever, cranial nerve deficits, loss of strength [11,12,13,14]. MRI is gold standard for the diagnosis of intracranial aspergillosis abscess. Radiological findings of abscess include hemorrhage, infaction, edema, peripheral ring-style contrast retention. These lesions are *iso*-hypointense in T1-weighted MRI series and heterogeneous, hypointense or hyperintense in T2-weighted series. Peripheral ring-style enhancement may be seen in post-gadolinium images, but necrosis may also be seen in these lesions [2,4,6].

The treatment of patients with intracranial aspergillosis should be planned with multidisciplinary approach. Oral or intravenous antifungal agents are important for medical treatment [15]. In invasive aspergillosis, surgical excision is the most important step



Fig. 5b. No lesion can be seen after surgery and systemic antifungal therapy (4) (From Neurosurgery, with permission).

of treatment. Surgery reduces pathogen burden and improves the efficacy of medical treatment. The treatment algorithm should be the combination of the surgical excision of the abscess with antifungal drugs and the removal of immunosuppressive agents. In the literature, articles on the administration of intracavitary amphotericin B following removal of the lesion are noteworthy. It should not be forgotten that the delivery of antifungal agents through the blood-brain barrier is limited and thus can not reach adequate concentration in the aspergillus abscess. A case of intracavitary amphotericin B administration was reported by Letscher et al. In this report, the aspergillus abscess was developed after head trauma in an immunologically normal patient and 5 mg/ml of amphotericin B was administered into the cavity following the abscess drainage. After this treatment, the patient had been alive for 5 years [16]. Camarata et al. operated on left temporal aspergillosis abscess and applied intracavitary amphotericin B and they stated that the patient was alive 6 years after the treatment. Again, this treatment has been shown to prevent side effects of antifungal drugs [12]. Elgamal et al. performed similar treatment modality to two cases. In addition, they administered intracavitary treatment for 5 weeks by Ommaya reservoir, and they reported long-term survival of the patient [17]. However, it is an optimistic idea to link the long survival time of these three cases to intracavitary drug administration. Özçelik et al. performed intracavitary amphotericin B administration after surgical excision of aspergillosis abscess in a case with lymphoblastic leukemia [18]. They reported that the abscess was totally treated, but the patient was lost due to immunodeficiency. This case demonstrates the efficacy of intracavitary amphotericin B in the treatment of abscess, but it also showed that survival is not only depend on abscess treatment.

In the literature, there are many articles on the positive results of intracavitary amphotericin B administration, and some of these reported that the long-term results are similar to other treatment modalities [19]. Ellenbogen et al.'s article is valuable for the evalu-

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ation of medical and surgical treatments of cerebral aspergillosis [2]. Although the efficacy of intracavitary drug administration was shown, there are not enough cases and data to produce a definite conclusion [2]. We agree with these authors and case series are not enough to draw major clinical outcomes because of no control groups to compare the results. In our report, we presented 3 cases of intracavitary amphotericin B administration following the excision of intracranial aspergillus abscess. In 2 cases, long-term survival was achieved while one patient was lost in the early postoperative period.

The major limitation of this report is very small number of patient for a major conclusion on the surgical treatment of intracranial aspergillosis. The second limitation is the lack of control group to compare the efficacy of intracavitary amphotericin B with surgeries without topical amphotericin B administration.

4. Conclusion

Intracavitary amphotericin B administration may be used as adjunct to the surgical excision of intracranial aspergillosis abscess. This treatment may contribute to the improvement of patient and/ or to the prevention of recurrence of abscess. But its effect on the survival time is still unknown. The most important cause of mortality is opportunistic infections and multi-organ failure developed afterwards. Comparative clinical series are needed to draw major clinical outcomes for this treatment modality.

5. Funding

No funding was received for this research.

6. Conflict of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patentlicensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

7. Ethical approval

For this type of study formal consent is not required.

8. Informed consent

Informed consent was obtained from all individual participants included in the study.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jocn.2018.02.018.

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