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Case Report

Surgical treatment of ruptured right middle cerebral artery mycotic aneurysm and central nervous system aspergillosis: Clinical case and literature review

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ABSTRACT

Background: Central nervous system (CNS) aspergillosis is more often met in patients with expressed immune suppression. Still, in 50% of cases of meningitis caused by Aspergillus spp., it is observed in patients without expressed immune suppression. The prognosis of CNS aspergillosis is unfavorable with the general rate of lethality around 70%.

Case Description: Clinical case of a 58-year-old man who developed an Aspergillus abscess in the chiasmosellar region and an associated mycotic aneurysm of the right middle cerebral artery (MCA) and intracerebral hemorrhage. Microsurgical clipping of the fusiform-ectatic aneurysm of the right MCA in the conditions of rupture was performed. An extra-intracranial micro anastomosis was formed on the right. An open biopsy of the neoplasm in the chiasmosellar region was made. The neoplasm was yellow and destroyed the bone plate of the skull base. Biopsy results: Mycotic lesion (aspergillosis). The analysis of surgical treatment for mycotic aneurysms in the acute period of hemorrhage in patients with aspergillosis revealed a high rate of lethality. The issue of the feasibility and effectiveness of complicated revascularization interventions in the patients with hemorrhage and aspergillosis remains unsolved.

Conclusion: The lack of generally accepted tactics of the treatment of this pathology requires further studies and systemic analysis. A high risk of the lethal outcome in patients with invasive mycotic infection and rupture of mycotic aneurysm highlight the importance of timely diagnostics and the beginning of antimycotic therapy. WThe issue of the evaluation of the revascularization methods effectiveness in patients after surgical treatment of a mycotic aneurysm associated with cerebral aspergillosis remains poor.

Keywords: Aspergillosis, Bypass, Ruptured aneurysm

INTRODUCTION

Central nervous system (CNS) aspergillosis is more often met in patients with expressed immune suppression. Still, in 50% of cases of meningitis caused by Aspergillus spp., it is observed in patients without expressed immune suppression. [3] CNS aspergillosis can develop in patients with the infection spread to paranasal sinuses via the iatrogenic or hematogenic pathway in patients with pulmonary aspergillosis. [4] The prognosis of CNS aspergillosis is unfavorable with the general rate of lethality around 70%. [11] In many patients, the identification of Aspergillus spp. as a causative

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agent can be made only retrospectively after the patient's death, which highlights diagnostic difficulties associated with this condition. [8] It should be mentioned that early diagnostic of aspergillosis leads to an increase in the overall survival rate. We presented a clinical case of a 58-year-old man who developed an Aspergillus abscess in the chiasmosellar region and an associated mycotic aneurysm of the right middle cerebral artery (MCA) and intracerebral hemorrhage. The goal of this work is to highlight the importance of timely diagnostics and the beginning of antimycotic therapy and high risk of the lethal outcome in patients with invasive mycotic infection and rupture of mycotic aneurysm. The issue of the evaluation of the revascularization methods effectiveness in patients after surgical treatment of a mycotic aneurysm associated with cerebral aspergillosis remains poor.

CLINICAL CASE

Patient X. 58 years old

The patient noticed a persistent decrease in the body weight by 8-10 kg within a month. He underwent examination for a decrease in the quality of vision (OD -0.1, OS -0). Brain magnetic resonance imaging (MRI) revealed a mass lesion in the chiasmosellar region [Figure 1]. The oncologic screening did not reveal extracranial pathology. Differential diagnosis was performed at the neuro-oncology rounds and an infectious-inflammatory process was suspected.

The patient's condition worsened when he felt a sudden headache and left extremities weakness. The patient was urgently hospitalized at the Burdenko Neurosurgical Center, Moscow, Russia. Computed tomography angiography (CTA) of the head revealed subarachnoid-parenchymal hemorrhage (around 40 ml) with the formation of an intracerebral hematoma of the right frontotemporal lobe. Besides, multi-slice CTA showed a fusiform aneurysm of the M2 branch of the right MCA [Figure 2]. MRI revealed an increase in the size of a mass lesion in the chiasmosellar region.

The examination performed in the resuscitation unit showed a decrease in consciousness to stupor, left-sided hemiparesis (score 3), and expressed visual impairments. Hyponatremia (128 mmol/l) and hyperglycemia (14.1 mmol/l) were revealed. Hormonal therapy-associated correction of fluid and electrolyte disorders with the improvement was observed (the level of consciousness increased to light stupefaction).

During the comparison of the obtained MRI data and the association of the mass lesion with the sphenoid sinus, an infectious-inflammatory process was suspected. Nevertheless, considering the vital indications, an urgent microsurgical intervention for fusiform aneurysm of the right MCA was performed. Considering the localization and morphological peculiarities of the aneurysm, and acute period of hemorrhage, endovascular treatment was not recommended. The patient was prepared for microsurgical clipping of the aneurysm.

Microsurgical clipping of the fusiform-ectatic aneurysm of the right MCA in the conditions of rupture was performed. The manipulation was carried out under bispectral index neuromonitoring and ultrasonic dopplerography control of the blood flow. An extra-intracranial microanastomosis (EICMA) was formed on the right. An open biopsy of the neoplasm in the chiasmosellar region was made.

External ventricular drainage (EVD) was placed. Pterional trepanation with an infratemporal bone resection was performed from the arciform incision of the skin in the right frontotemporal area. The Dura mater was moderately tensed. It was opened with a semicircular incision to the forehead. In the area of the Sylvian fissure and the base, the signs of hemorrhage were visible. The brain was barely pulsing. In the pole of the temporal lobe on the right, 1.5 cm encephalotomy was performed. The hematoma cavity was opened. It contained soft clots with blood that were removed easily by suction and washing. Gradually, all available fragments of the hematoma (around 40 ml) were removed. The brain started to pulse. The surgeons opened

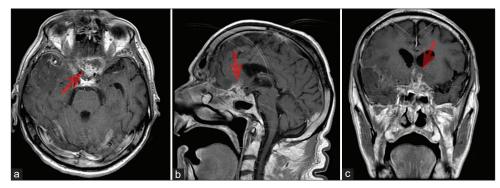


Figure 1: (a-c) Axial, sagittal, and frontal magnetic resonance imaging projection of the brain T1 + contrasting agent: the picture of the area of pathologic contrasting of the chiasmosellar region (red arrow) with elevated parameters of the perfusion. Probably, the picture of inflammatory (infectious?) alterations. Tumor presence is unlikely.

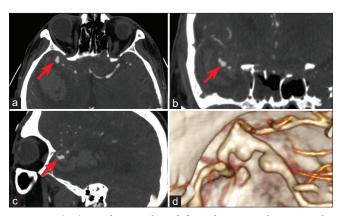


Figure 2: (a-c) Axial, sagittal, and frontal computed tomography angiography projection of the head: Fusiform, partially thrombosed aneurysm of the right middle cerebral artery (MCA) (red arrow). A 3D reconstruction showed a contrasting part of the aneurysm in the area of M2 of the right MCA in the form of two bulgings with a wide neck.

the carotid cistern. Blood-containing liquor appeared. Stepwise, the Sylvian fissure was dissected for the isolation of the sclerosed internal carotid artery (ICA) and elongated and twisted MCA. The MCA was fusiform expanded in the area of the bifurcation. In the area of the bifurcation, a partially thrombosed aneurysm (around 1.5 cm in diameter) was revealed cuffed by an "old" hematoma with a capsule. The M1 segment was isolated. During the dissection of the aneurysm, arterial hemorrhage started. The rupture was revealed in the sidewall of the aneurysm. The hemorrhage was controlled by the suction and stopped by the application of the fragment of Tachocomb and gauze. Numerous scars and the sclerosed hematoma capsule indicated a hemorrhage occurred long ago. Major technical difficulties were faced in the isolation of the aneurysm that was a hemisphere-shaped ectasia on the sidewall of the twisted and expended MCA bifurcation. During the isolation of one of the branches of M2, another aneurysm rupture occurred associated with a temporary clipping of the M1 segment ($2 \times 3-4$ min). The aneurysm was clipped with two standard clips Neuron. The ultrasonic dopplerography showed that one of the M3 branches functioned (20 cm/s), and the other coupled branch did not function despite the visually patent bifurcation lumen. Applications of papaverine, intra-arterial injection of prolapse, and reposition of the clips were not successful. The trapping of the M3 branch and arteriotomy (3 mm) were performed above the thrombosed M3 branch. It was revealed that the arterial wall was thickened and sclerosed. There was a newly formed clot in the lumen. The clots were removed, and the arteries were washed with an arterial microcatheter, which did not restore the blood flow. The artery was sutured, and the hemostasis was restored. EICMA was placed to compensate the blood flow. The surgeons isolated the frontal branch of the superficial temporal artery and the recipient

artery, the distal segment of the thrombosed M3 branch. The microsurgical technique was used to make an endto-side anastomosis with Prolene 9-0. The checking of the anastomosis showed good blood flow (40 cm/s).

Further, the biopsy of resected aneurysm wall and soft tissue lesion in the chiasmosellar region were performed. The neoplasm was yellow and destroyed the bone plate of the skull base. A thin capsule of the neoplasm and several soft nonvascular tissue bioptates were taken. Biopsy results showed invasive fungal elements from outer to the inner side in the aneurysmal wall and numerous filamentary infiltrates with an acute angle branching confirming to the morphology of mycotic lesion (aspergillosis) [Figure 3].

Despite satisfactory functioning EICMA, an ischemic stroke event developed in the basin of the right MCA artery after the clipping of the mycotic aneurysm. MRI and magnetic resonance arterial spin labeling perfusion on the 2nd day after the surgery [Figure 4]. Conservative therapy was performed. The patient's condition remained stable: The level of consciousness was deep stupefaction, left-sided hemiplegia. Artificial lung ventilation and intensive therapy were performed in the conditions of the intensive care unit.

A parenchymatous intracranial pressure (ICP) sensor was implanted. The ICP was monitored. On the 3rd day after the surgery, a persisting increase in the ICP of more than 30 mmHg was observed for an hour that was not resolved by conservative methods (EVD, osmotic diuretic, deep sedation).

Considering the dynamics of intracranial hypertension, an increase in the brain edema, and dislocation revealed by computed tomography (CT) [Figure 5], a decision was made to perform decompressive trepanation with the preservation of EICMA. Urgent surgery was performed. Decompressive trepanation in the fronto-parietotemporal area on the right combined with dura mater plasty with a periosteal flap was performed. After the surgery, the patient's condition stabilized. There was no expressed increase in the ICP. Intensive therapy was performed. The functioning of EICMA was shown by the results of the duplex ultrasonic study.

Despite the performed conservative therapy and relative stabilization of the patient, sub-febrile fever persisted for a month. Suddenly, exudation presented from under the skin flap. MRI of the brain [Figure 6] showed signs of the infectious-inflammatory process, empyema of the epidural and subdural spaces. Vast foci of a cerebrovascular accident were observed in the basins of the MCA on both sides. ICA occlusion visualized on the left. Signs of ventriculitis were revealed. Flow-rinsing drainage of the epidural space was performed along with systemic antibacterial and fungicide therapies.

antibacterial and fungicide therapy, inflammatory-exudative process resolved. Within a month,

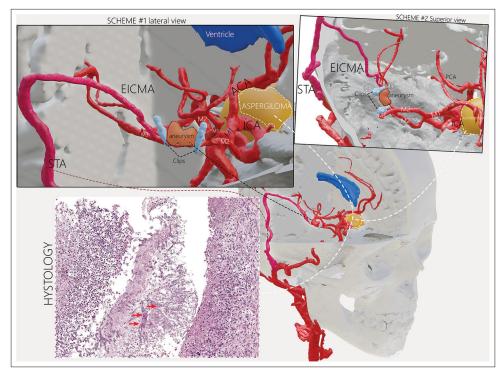


Figure 3: The scheme of the surgical intervention: Trapping-clipping of the aneurysm, extra-intracranial microanastomosis of the superficial temporal artery, and the M3 branch of the right middle cerebral artery. The location of the aspergilloma in the chiasmosellar region. The microscopic study of the biological material revealed the fragments of the connective tissue with chronic granulomatous inflammation and branching hyphae of the fungus (red arrow).

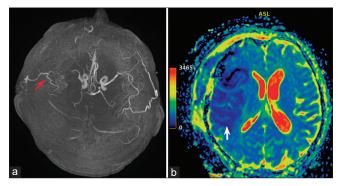


Figure 4: (a) Magnetic resonance angiography of the head on the 2nd day after the surgery. Extra-intracranial microanastomosis on the right functions (red arrow). (b) Arterial spin labeling magnetic resonance perfusion: Signs of ischemic events in the right frontal lobe (white arrow).

an observation and recreational therapy were performed that did not reveal the signs of infectious-inflammatory alterations. The patient was in the condition of low consciousness. He was transferred to the rehabilitation center without the signs of inflammation and underwent recreational therapy for several months without any expressed neurological dynamics. The patient died several months after the discharge from the rehabilitation center.

DISCUSSION

Invasive aspergillosis can be complicated by the formation of secondary intracranial mycotic aneurysms. [2] They can result from a direct fungal invasion from the adjoining infectious foci or hematogenic spread, primarily, from the lungs. Besides, one of the causes of aspergillosis spread to the CNS, described in published literature, is neurosurgical intervention.[13] Aspergillus fungi bind with a wall of cerebral vessels and cause its inflammation, which leads to thrombosis, dilation and rupture, and the formation of a mycotic aneurysm. According to the published data, around 60% of patients with histologically verified aspergillosis have a clinical trial of a mycotic aneurysm, cerebral infarction, and multiple infectious granulomas.^[2,8,13] The production of elastase by the fungi contributes to the destruction of elastin and invasion to the arterial wall. Such focal inflammatory response can lead to the formation of an aneurysm, its rupture, and the development of subarachnoid hemorrhage.

Timely diagnostics of CNS aspergillosis is a complicated clinical task. It is confirmed by the fact that only in 56% of patients, CNS aspergillosis is diagnosed during life.[1] The presence of fungal infection in immune-competent patients (patients without immune deficiency) is suspected only in the lack of effect after standard antibacterial therapy against

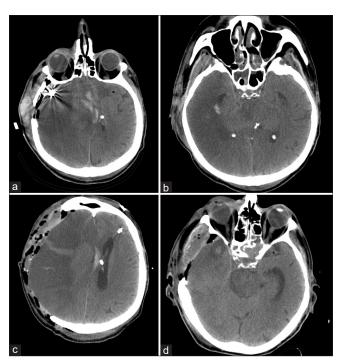


Figure 5: (a and b) computed tomography (CT) of the head on the 3rd day after the surgery. Hemispheric ischemic impairments on the right, expressed edema and dislocation of the brain. (c and d) CT of the head after decompressive trepanation. Expressed brain prolapse into the trepanation defect. Cisterna ambiens is visualized.

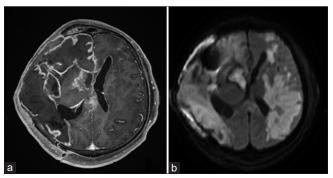


Figure 6: (a) Magnetic resonance imaging of the head with contrasting: Signs of expressed leptomeningitis with the formation of epidural empyema in the right frontal region. (b) Diffusion-weighted imaging: Vast foci of cerebrovascular accident are visualized in the basins of the middle cerebral artery from both sides. The internal carotid artery is occluded on the left.

typical bacterial agents that cause meningitis. In such cases, certain neuroimaging signs (ischemia in the basal ganglia and/or thalamus, subarachnoid hemorrhage, abscess with a ring-shaped area of contrasting agent accumulation, infection of paranasal sinuses) typical for CNS aspergillosis facilitate the diagnostic of this pathology. [12]

CT and MRI signs of this disease are non-specific, which complicates the differentiation analysis of other mass lesions. CT scans show invasive aspergillosis as a well-isolated, heterogeneous, and hyperdense mass or heterogeneous infiltrate formation. Besides, there are signs of hyperostosis and osteolysis of the adjoining bone tissue. The presence of calcificates with a density of more than 2000 HU is a typical sign of aspergillosis. [2] T1-weighted images of invasive orbital aspergillosis usually have iso or hypointensive signals. T2 images have a hypointensive signal. The study with a contrasting agent shows a heterogeneous character of its accumulation. CT and cerebral angiographies are necessary for the diagnostic and dynamic control of secondary mycotic aneurysms. CT and MRI data combined with the specified signs indicate a high probability of aspergillosis. However, the diagnosis is verified only based on the results of the histological study.[2-4]

Often, the morphological study can provide false-negative results. Thus, it is recommended to take bioptates from several areas of the mass lesion. The involvement of a large amount of liquor and the performance of repeated microbiological studies can provide the possibility of the infectious agent identification.[8]

Alternative "non-culture-based" methods of verification of the infectious agent have higher sensitivity and specificity. They include galactomannan test that detects the antigens to the fungal cell walls and is widely used for the diagnostic of invasive aspergillosis and monitoring of the effectiveness of pharmacotherapy. The manufacturer recommends using the test for liquor. There are no respective standardized normative parameters. However, Antinori et al. demonstrated 87% sensitivity of this test in 15 patients with CNS aspergillosis.[1] The same level of sensitivity was demonstrated in small samplings.^[7] Another effective alternative method of the study is the detection of β -D-glucan that is also present in fungal cell walls of *Aspergillus*.^[10] There are a limited number of cases that describe its application and demonstrate significant results. The drawback of this method is low specificity in the diagnostics of systemic aspergillosis. Besides, one of the diagnostic options is polymerase chain reaction (PCR) for Aspergillus DNA or amplification areas of the internal transcribed spacer-2. Several studies described the application of this method for the diagnostics of CNS aspergillosis and demonstrated controversial results on the sensitivity of this method. [6,9] Considering the low sensitivity of culture-based methods, PCR can be used in addition to antigen tests in the diagnostic and verification of Aspergillus fungal infection.[6]

There are limited publications on this clinical issue. The majority of them are single clinical cases. We looked through literature for studies since 2015. They are summarized in [Table 1].

Radotra et al.[7] describe a clinical case with a 38-year old patient who underwent standard transsphenoidal removal

Table 1: Surgical treatment outcome.						
Author	Aspergillosis localization	Aneurysm localization	Aneurysm rupture	Conservative treatment	Surgical treatment	Treatment outcome
Yamaguchi <i>et al.</i> , 2016 ^[7]	Sphenoid sinus	Ophthalmic aneurysm of the right ICA	-	Amphotericin B Replaced with Micafungin before surgical treatment; Itraconazol – after surgery	ICA trapping+ECA-M2 (radial artery graft) + STA-M4+STA-ACA	Persisting cognitive impairmen
Winterholler <i>et al.</i> , 2017 ^[5]	Sphenoid sinus (pituitary adenoma)	Fusiform aneurysm of the basilar artery bifurcation	Massive SAH	Voriconazole	Flow diversion stent	Lethal
Radotra <i>et al.</i> , 2015 ^[12]	Sphenoid sinus (after pituitary adenoma removal)	Basilar artery bifurcation	Massive SAH and IVH	Only antibacterial therapy (Vancomycin and Meropenem)	External ventricular drainage	Lethal
Sangrador-Deitos <i>et al.</i> , 2020 ^[4]	Fungal shunt infection (FSI)	Right middle cerebral artery bifurcation	Massive SAPH	Amphotericin B and fluconazole	-	Lethal
Tambuzzi <i>et al.</i> , 2019 ^[3]	Mastoid cells (after the removal of vestibular schwannoma)	Artery mouth of the posterior inferior cerebellar artery	Massive SAH	-	-	Lethal

SAPH: Subarachnoidal parenchymal hemorrhage

of pituitary adenoma. Three weeks after the surgery, the patient developed fever with cerebrospinal fluid rhinorrhea and applied repeatedly to the hospital. Three weeks after the admission to the hospital, the patient suddenly lost consciousness. CT images showed massive subarachnoid hemorrhage and intraventricular hemorrhage. Despite the performed therapeutic measures, the patient died. An autopsy revealed a rupture of a mycotic aneurysm in the bifurcation of the basilar artery.

Yamaguchi et al.[13] described a clinical case of a 79-year old patient who received antituberculosis therapy for tuberculosis recurrence. Two weeks after, significant cognitive impairments developed. Aspergillus antigens were detected in the liquor. MRI revealed signs of fungal meningoncephalitis caused by the invasion of Aspergillus from the sphenoidal sinus. After antimycotic therapy [Table 1], the size of aspergilloma was reduced. However, SCT angiography revealed de novo aneurysm of the ophthalmologic segment of the right ICA and the stenosis of the postcommunicant segment of both anterior cerebral arteries (ACAs). It was also proved by the areas of hyperfusion in the basins of these arteries revealed by single-photon emission CT. A combined microsurgical study was performed. During the surgery, because of the high risks of intracranial dissemination of the

infecting agent, the surgeons refused to performed anterior sphenoidectomy. According to the control study, anastomoses were patent. There were no new areas of ischemia. Perfusion in the basin of the right ACA improved. Antimycotic therapy was continued. The patient was discharged on day 55 after the surgery with persisting cognitive impairments.

Winterholler et al.[12] also described a clinical case of a patient with pituitary adenoma and CNS aspergillosis. The patient was admitted to the hospital with fever, dysarthria, diplopia, and walking impairment. CT and MRI showed signs of ischemia in the area of the left thalamus. Multiple culturebased tests did not reveal signs of microorganism invasion in the liquor. Hence, empiric antibacterial therapy was performed that did not provide any significant positive effect. Control studies revealed the signs of brainstem infarction, sphenoiditis, and an increase in the size of the mass lesion in the region of the Turkish saddle. Mycotic infection was suspected. During transsphenoidal biopsy, the condition of the patient suddenly worsened to a deep coma. CT revealed a massive subarachnoid hemorrhage. Cerebral angiography showed a rupture of a fusiform aneurysm in the bifurcation of the basilar artery. A stent was placed in the vascular lumen. However, the patient's condition was severe. MRI showed signs of infarction in the basin of the ACA and posterior

cerebral artery, in the midbrain and cerebellum. The patient died 18 days after the admission. CNS aspergillosis was verified by the results of the autopsy.

Rare localization of aspergillosis was described by Tambuzzi et al.[11] The patient applied to the hospital with a fever on the 15th day after the removal of vestibular schwannoma. During the examination, the patient's state suddenly worsened, which resulted in a fulminant lethal outcome. The autopsy revealed massive intracerebral hemorrhage from the fusiform aneurysm in the posterior inferior cerebellar artery mouth. A mycotic genesis (Aspergillus spp.) of the aneurysm was verified by the results of the histological study.

Sangrador-Deitos et al.[8] described a clinical case of CNS aspergillosis in a patient with hydrocephaly after ventriculoperitoneal shunting. The shunt was removed because of its failure. The culture-based study of the fragment of the shunting system revealed Aspergillus terreus. 2 weeks after the therapy, a sudden worsening of the condition occurred. CT revealed massive hemorrhage in the right operculoinsular zone from the saccular aneurysm in the bifurcation of the MCA. Because of an unfavorable prognosis, surgical treatment was not performed and the patient died on day 5 after the verification of the diagnosis.

The experience of endovascular treatment in the acute period after the hemorrhage caused by CNS aspergillosis is scarce and required further studies. It is limited by single cases of deconstructive interventions in patients with mycotic pseudoaneurysm.^[5] The analysis of surgical treatment for mycotic aneurysms in the acute period of hemorrhage in patients with aspergillosis revealed a high rate of lethality. The issue of the feasibility and effectiveness of complicated revascularization interventions in patients with hemorrhage and aspergillosis remains unsolved. The lack of generally accepted tactics of the treatment of this pathology requires further studies and systemic analysis.

CONCLUSION

Mycotic aneurysm caused by Aspergillus infection is a rare and dangerous complication associated with a high rate of lethality. A high risk of the lethal outcome in patients with invasive mycotic infection and rupture of mycotic aneurysm highlight the importance of timely diagnostics and the beginning of antimycotic therapy. The issue of the evaluation of the revascularization methods effectiveness in patients after surgical treatment of a mycotic aneurysm associated with cerebral aspergillosis remains poor.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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