Journal of Neuroinfectious Diseases
ISSN: 2314-7326

Case Report Open Access

Acute Stroke Due to *Cunninghamella bertholletiae* Orbital Cellulitis – A Case Report and Review of the Literature

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Abstract

Introduction: We present a case with repeated cerebral infarction by thrombotic fungal mycelium (*Cunninghamella bertholletiae*) in the right and left pre-stenosed internal carotid artery.

Case: A 72-year-old female patient with a myelodysplastic syndrome presented with a right orbital swelling and a loss of vision. A computer tomography scan and magnetic resonance imaging were suspicious of orbital cellulitis. An orbital decompression was performed. After surgery, the patient developed a hemiparesis on the left side. A computer tomography revealed an internal carotid artery occlusion on the right side. A thrombectomy was performed successfully. The following days a central artery occlusion on the right eye was diagnosed. A lumbar puncture revealed a highly increased white blood count matching to the diagnosis of a meningoencephalitis. On the fourth day of treatment in the neurology department, the patient developed fixed and dilated pupils. A computer tomography showed new bilateral anterior cerebral artery infarctions and infarction of the entire territory of the left middle cerebral artery. Intensive care treatment was terminated. The autopsy found an orbital cellulitis with invasive mycosis caused by mould. Internal transcribed spacer (ITS) sequencing revealed *Cunninghamella bertholletiae* in the material obtained from the orbit and the left internal carotid artery. Retrospectively, sepsis of thrombotic fungal mycelium due to increased pathological coagulation repeatedly resulted in arterial embolism.

Conclusion: In immunosuppressed patients, rare pathogens can cause sepsis and septic complications. A calculated antifungal therapy should be considered in cryptic cases of meningoencephalitis.

Keywords: *Cunninghamella bertholletiae*; Septic embolism; Orbit; Sepsis; Stroke

Case presentation

Introduction: We present a case with repeated occurrence of cerebral infarction in the right and left pre-stenosed internal carotid artery due to thrombotic fungal mycelium (*Cunninghamella bertholletiae*).

Case description: A 72-year-old female patient was admitted to the eye clinic due to right orbital swelling and a loss of vision. Medical history included a myelodysplastic syndrome with a blast excess and a low-grade T-cell lymphoma. With the suspected diagnosis of posterior ischemic optic neuropathy, a high dosed cortisone therapy was started. A computer tomography scan and magnetic resonance imaging of the orbit were suspicious of orbital cellulitis, and the patient was transferred to an ear, nose, and throat clinic, where orbital decompression was performed under antibiotic therapy with ampicillin and sulbactam. An hour after surgery, the patient presented with hemiparesis on the left side. A computer tomography revealed an internal carotid artery occlusion on the right side. The patient was transferred to the neurology department of the university hospital in Essen, Germany. At admission, the patient was awake with hemiplegia on the left side, a facial palsy on the left side, and pronounced swelling in the right orbital area. The laboratory tests revealed a pancytopenia with a white blood count of 2.38 /nL, a haemoglobin of 6.5 g/dL and a platelet count of 90 /nL. The C-reactive protein (CRP) was 7.3 mg/dL (normal range <0.5 mg/dL). Procalcitonin showed normal values. A thrombectomy was successfully performed in general anaesthesia (Figure 1).

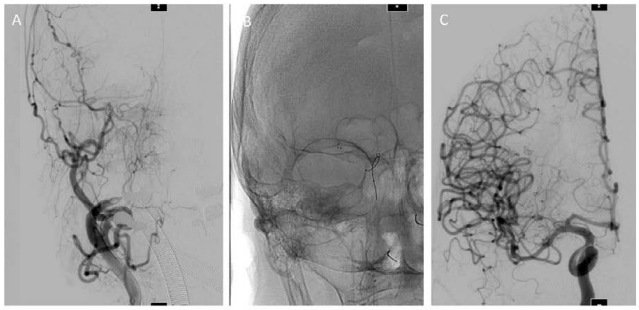

Figure 1: Thrombectomy. Digital subtraction angiography shows occlusion of right internal carotid artery (A), after combined mechanical thrombectomy with Stent retriever und aspiration catheter (B) the complete territory of the internal carotid artery is reperfused (C).

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Received: 20-Jan-2022, Manuscript No. JNID-22-51976; **Editor assigned:** 22-Jan-2022, PreQC No. JNID-22-51976 (PQ); **Reviewed:** 05-Feb-2022, QC No. JNID-22-51976; **Revised:** 10-Feb-2022, Manuscript No. JNID-22-51976 (R); **Published:** 04-Mar-2022, DOI: 10.4172/2314-7326.1000383

Citation: Oster C, Steinborn JK, Blau T, Rath PM, Schmid KW, et al. (2022) Acute Stroke Due to *Cunninghamella bertholletiae* Orbital Cellulitis – A Case Report and Review of the Literature. J Neuroinfect Dis 13: 383.

Because of recent surgery and low platelet count, intravenous thrombolysis was not administered. The ventilated patient was transferred to the neurological intensive care unit. In the control imaging on the next day, only small infarct demarcation of the right rostral basal ganglia was detected. The ophthalmologist diagnosed a central artery occlusion of the right eye with a rock-hard bulb. Assuming a transorbital meningoencephalitis, a lumbar puncture was performed. There was a highly increase in leukocytes mostly granulocytes (1794 / µL) and in interleukin-6 (54631 pg/mL) in cerebrospinal fluid (CSF). The CRP increased to 29.6 mg/dL. A calculated antibiotic therapy with ceftriaxone, metronidazole and flucloxacillin was started. Blood and cerebrospinal fluid testing remained culturally negative. Serologically, there was no sign of syphilis and Lyme disease. The patient developed a septic shock, and weaning was at hold. Approximately 80 hours after admission, the patient suddenly presented with dilated and fixed pupils. A computer tomography revealed new bilateral anterior cerebral artery infarctions and infarction of the entire territory of the left middle cerebral artery with clear signs of elevated intracranial pressure. Due to the poor prognosis, the intensive care treatment was terminated. The patient died 8 days after first symptoms of orbital swelling. (Figure 2)

An autopsy was arranged to clarify the orbital process. The autopsy found an orbital cellulitis with invasive mycosis caused by mould. Internal transcribed spacer (ITS) sequencing revealed *Cunninghamella bertholletiae* in the material obtained from the orbit and the left internal carotid artery. In retrospect, sepsis of thrombotic fungal mycelium led to increased pathological coagulation and repeated arterial embolism in the right and left pre-stenosed internal carotid artery. This resulted in extensive bilateral infarcts with a consecutive increase in intracranial pressure.

Discussion

Cunninghamella bertholletiae (*C. bertholletiae*) is a worldwide occurring mould of the order Mucorales and the family *Cunninghamellaceae*. [1, 2] Within this family, *C. bertholletiae* is responsible for most human-pathogenic infections. Other human pathogenic *Cunninghamellaceae* are *Cunninghamella elegans* [3], *Cunninghamella blakesleeana* [4] and *Cunninghamella echinulate* [5]. Infections with Mucorales show a very variable incidence depending on geographical location and population [6]. *Cunninghamellaceae* infections account for about 5% of all Mucorales infections in Europe [7].

C. bertholletiae is an opportunistic pathogen. The main risk factor for an infection is therefore immunosuppression as in the context of an underlying haematological disease or post organ transplantation [6]. Very rarely immunocompetent patients fall ill [8]. The patient presented had a history of a blast excess due to a myelodysplastic syndrome and a low-grade T-cell lymphoma. In addition, the patient received a high dosed cortisone therapy due to the suspected diagnosis of posterior ischemic optic neuropathy. She therefore had risk factors for opportunistic infections.

The upper and lower respiratory tract is most frequently affected by an infection with *C. bertholletiae* via inhalation. Contamination of wounds occurs significantly less frequently [1]. Like other Mucorales, *C. bertholletiae* shows an angio-invasive behaviour, so that the pathogen can spread via the bloodstream and per continuitatem [1, 9]. Rhinoorbitocerebral infections account for 50% of infections in other Mucorales, but are less common in *C. bertholletiae* with 13% [1]. In this case, however, an orbital cerebral infection was present with histological evidence of fungal hyphae in the orbit, both internal carotid artery and leptomeningeal vessels. The lung showed no autoptic evidence of fungal hyphae.

Depending on the location of the invasive Mucorales infection, different symptoms may occur. While the pulmonary localization manifests itself by fever and respiratory symptoms. In rhino-orbital-cerebral disease, unilateral facial swelling, skin necrosis, proptosis, sinusitis and amaurosis may develop. An osseous destruction of the orbit as in the case presented here is possible. The invasion of the fungus of orbit, eye and brain can be visualized by CT and MRI morphology [1, 6].

The angio-invasive growth pattern of *C. bertholletiae*, which can lead to dissemination of the pathogen and thromboembolisation with infarction, has been described several times in the literature [10]. In this context, cerebral involvement also resulted in strokes as in the case presented here [11-13].

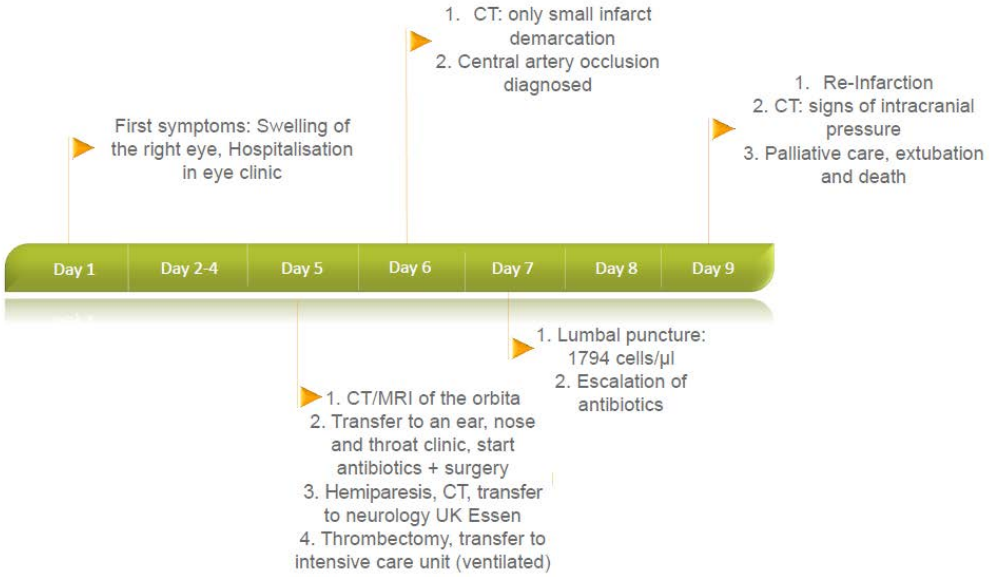

Figure 2: Timeline. The timeline shows the events in chronological order from first symptoms of eye swelling until the death eight days later. CT: computer tomography, MRI: magnetic resonance imaging, UK: University hospital

Table 1: Overview of previously described C. bertholletiae infections with proven or highly suspected* cerebral involvement.

Reference	Age (years) Sex	Underlying conditions	Initial symptoms	Diagnosis	Outcome
Brennan 1983 [11]	70 male	Thalassemia minor Sideroblastic anaemia Iron overload	Sinusitis Facial Cellulitis Facial Pain Unilateral decreased hearing	Via culture	Died
Kolbeck 1985 [12]	40 male	Renal transplant nephrectomy after allograft rejection	Fever dyspnoea	Via culture post mortem	Died
Nimmo 1988 [14]	19 female	Morbus Wilson Liver transplant	Fever	Via culture post mortem	Died
Ortín 2004 [10]	44 male	T-Cell acute lymphoblastic leukaemia	Thoracic and substernal pain dyspnoea	Via culture* post mortem	Died
Righi 2008 [15]	41 male	Acute myeloid leukaemia	Fever Unilateral facial oedema	Via culture*	Died
Mayayo 2009 [13]	50 male	T-Cell acute lymphoblastic leukaemia	Hemiparesis	Via culture post mortem	Died
Mayayo 2009 [13]	42 male	Acute myeloid leukaemia	Fever Pleuritic chest pain	Via culture post mortem	Died
Su 2016 [16]	13 female	Acute lymphoblastic leukaemia	Cough Haemoptysis Dyspnoea	Via polymerase-chain-reaction*	Died
Hiramoto 2020 [17]	23 male	Osteosarcoma	Fever Unilateral ptosis Loss of vision Unilateral mydriasis Disorientation Dyspnoea	ITS-Sequencing* post mortem	Died

5,8SR: 5‘- TCG ATG AAG AAC GCA GCG- 3‘
LR1: 5‘- GGT TGG TTT CTT TTC CT- 3‘

Figure 3: Primer names and sequence in 5‘-3‘ direction.

The following table provides an overview of previously described *C. bertholletiae* infections with proven or highly suspected* cerebral involvement. (Table 1)

ITS sequencing was used to detect fungal hyphae of *C. bertholletiae* in the material obtained from the orbit and in the thrombotic material from the left internal carotid artery. During ITS sequencing, the ITS regions located within the eukaryotic rDNA are examined. The ITS regions show a high genetic polymorphism and can be used for species identification of for example Mucorales [18]. For the identification of *C. bertholletiae*, the 5.8 rDNA and ITS 2 region (LR1) (Figure 3) were examined by sequencing [19]. A polymerase chain reaction (PCR) product of 382 base pairs length was obtained. The product showed a sequence match of 90-96% with *C. bertholletiae* when searching with the National Center for Biotechnology Information Basic Local Alignment Search Tool (NCBI BLAST) (on August 5, 2020) [20]. (Figure 3)

Unlike *Aspergillus* or *Candida* spp., Mucorales cannot be identified by antigen detection. A commercial PCR is currently not available either. The detection can be done by cultural or histological evaluation. The evaluation of the morphology of Mucorales for genus or species identification is difficult. ITS sequencing represents an alternative [6].

The mortality rate of infections with *C. bertholletiae* is very high at 77% [1]. The global guideline for the diagnosis and management of mucormycosis issued by the European Confederation of Medical Mycology (ECCM) in cooperation with the Mycoses Study Group (MSG) and Education and Research Consortium (ERC) recommends rapid surgical debridement and antifungal therapy with liposomal amphotericin B 10 mg/kg bodyweight per day in suspected cases of infection with Mucorales and brain involvement. The material obtained during surgical debridement to control the disease can be examined histopathologically and microbiologically. Narrowing the spectrum of pathogens helps in the selection of antifungal therapy [6].

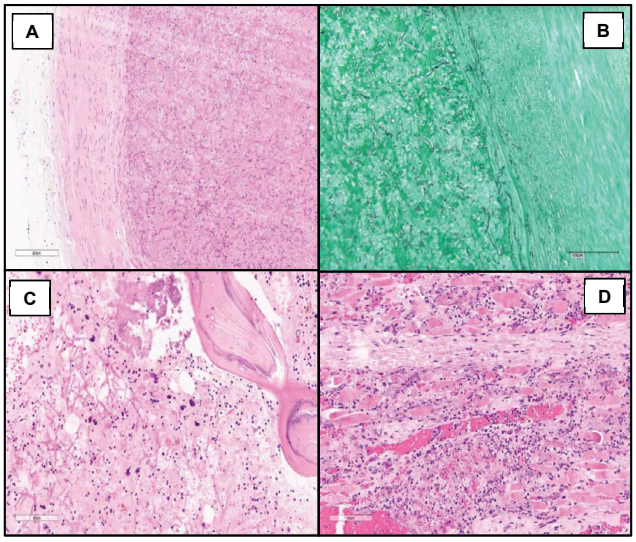

Figure 4: Histology of the autoptically obtained material in hematoxylin-eosin stain: (A) From the right internal carotid artery with thrombotic occlusion of the vascular lumen by the mycelium (magnification factor 10x) and (B) in Grocott's methenamine silver stain (magnification factor 20x). Material obtained from the orbit, showing necrotic bone (C) and skeletal muscle with surrounding inflammatory reaction (D) (magnification factor 20x) in hematoxylin-eosin stain.

In conclusion, rare pathogens should be looked at very closely in immunosuppressed patients with an infection. If there are thromboembolic events in immunosuppressed patients with meningoencephalitis, mould like *C. bertholletiae* should be part of differential diagnostics. A calculated antifungal therapy should be considered in cryptic cases of meningoencephalitis without proof of classic pathogens. (Figure 4)

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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