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Medical and surgical treatment of rhino-orbital-cerebral mucormycosis in a child with leukemia

Mette Levinsen [a], Jens Folke Kiilgaard [a,*], Carsten Thomsen [b], Steffen Heegaard [a,c], Kamilla Rothe Nissen [a]

[a] Department of Ophthalmology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
[b] Department of Radiology, Zealand University Hospital, Roskilde, Denmark
[c] Department of Pathology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

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ABSTRACT

Purpose: Rhino-orbital-cerebral mucormycosis (ROCM) is a rare opportunistic infection with a high mortality despite relevant treatment.

Observations: A 3-year-old girl under treatment for acute lymphoblastic leukemia developed periorbital swelling, ophthalmoplegia and a necrotic palatal lesion during a period of neutropenia. Imaging revealed sinusitis, pre- and postseptal cellulitis. The disease later progressed to cerebral involvement and orbital apex syndrome with complete ophthalmoplegia, ptosis and loss of vision. The patient was treated with systemic antifungal therapy, hyperbaric oxygen and extensive surgery. This included orbital exenteration, skull base resection, cerebral debridement with placement of an Ommaya reservoir for intrathecal administrations of amphotericin B (AmB) and in addition endoscopic sinus surgery with local AmB installation. Chemotherapy was safely continued after resolution of the ROCM and the patient remains in complete remission after 5 years.

Conclusion and importance: Patients with ROCM can be cured with aggressive multimodality treatment, including surgical intervention, even if in myelosuppression.

1. Introduction

Rhino-orbital-cerebral mucormycosis (ROCM) is an aggressive, rare and opportunistic infection typically seen in immunosuppressed or poorly controlled diabetes patients.[1] Mucormycosis is caused by fungi of the order Mucorales (class Zygomycetes) which are ubiquitous in nature and intrinsically resistant to several antifungal agents.[2] The fungus invades the sinonasal mucosa and may spread to the orbit via the ethmoidal sinuses and lamina papyracea. Based on the ability for angioinvasion, the fungal hyphae may extend to the cerebrum along the ophthalmic vessels or the cavernous sinus. The vascular invasion results in thrombosis causing infarction and necrosis of the involved tissues leading to decreased tissue penetration of systemic antifungal therapy. Treatment thus usually consists of systemic antifungals together with aggressive surgical debridement of infected tissue and reversal of predisposing conditions. Hyperbaric oxygen (HBO) may be given as adjuvant therapy.[3,4] ROCM typically presents in a rapidly fulminant manner with headache, fever, mucosal necrosis and ophthalmological findings such as ophthalmoplegia, proptosis, chemosis, decreased visual acuity, periorbital swelling and pain.[5] Despite early diagnosis and aggressive treatment, the disease carries a high mortality. Individualized multidisciplinary approaches are therefore recommended.[3] We report the successful treatment of ROCM in a 3-year-old child under treatment for acute lymphoblastic leukemia (ALL).

1.1. Case report

A 3-year-old girl was diagnosed with pre-B ALL and treated according to the Nordic Society for Pediatric Haematology and Oncology ALL-2008 protocol. After 4 weeks of induction therapy, she obtained complete remission. Six weeks after diagnosis (after completing 16 days of antibiotics due to an episode of febrile neutropenia with no recognized focus), the patient developed right-sided periorbital swelling and fever (defined as the first day of mucormycosis infection) (Fig. 1). The prophylactic fluconazole treatment was supplemented with broad-spectrum antibiotics and chemotherapy was paused. On day 4, the periorbital

* Corresponding author. Department of Ophthalmology, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, DK-2100, Copenhagen, Denmark.
E-mail address: Jens.Folke.Kiilgaard@regionh.dk (J.F. Kiilgaard).

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swelling had progressed to the left eye and fusidic acid eye drops were initiated. Examination on day 6 revealed hyperemia of the conjunctiva, chemosis and mildly restricted extraocular movements of the right eye. On day 7, the patient presented with areactive mydriasis, decreased abduction of the right eye and a white-brown lesion of the hard palate. Computed tomography (CT) revealed opacification of the right maxillary sinus and ethmoidal cells, 2-mm proptosis, edema of the periorbital soft tissue and enlargement of the rectus muscles of the right side consistent with pre- and postseptal cellulitis (Fig. 2A). The findings were suspected to be due to a fungal infection and fluconazole was switched to liposomal amphotericin B (L-AmB) and voriconazole. Examination on day 8 revealed resistance to retropulsion of the globe, possible loss of light perception of the right eye and an increase in anisocoria. The dilated right pupil was interpreted as a possible reversible affection of the third cranial nerve at the orbital apex. The patient underwent right-sided endoscopic sinus surgery with an opening to the maxillary sinus and ethmoid bulla. Microscopic examination of biopsies from the palate and nasal cavity revealed no sign of fungi. Canthotomy and medial wall orbital decompression were not performed due to the risk of further spread of the infection. During the following two days, there was progression to orbital apex syndrome with complete ophthalmoplegia, ptosis and visual loss of the right eye. Betaxolol eye drops were started on the right eye to improve the circulation of the optic nerve. Serum Aspergillus galactomannan antigen test was negative and blood, faeces and nasal swab cultures were negative for bacteria and fungi.

On day 10, biopsy culture from the palate and nasal cavity yielded growth of mould fungus. Magnetic resonance imaging (MRI) demonstrated edema and abnormal enhancement of the intracanalicular segment of the right optic nerve, involvement of the soft palate, tonsils, meninges and brain parenchyma with infarction in the temporal and frontal lobe of the right side. It was concluded that the visual impairment of the right eye was due to optic neuritis and the ophthalmoplegia of the right bulbus was due to inflamed meninges in the cavernous sinus and consequent affection of the cranial nerves III, IV and VI. Decompression of the optic canal of the right side was not performed as it was considered not to improve the visual acuity. Fundoscopy of the right eye on day 12 revealed a clear vitreous body, blurred disc margin and a creamy white infiltrate in the choroid compatible with chorioretinitis (Fig. 2B). The patient underwent a second right-sided endoscopic sinus surgery combined with right-sided inferior conchotomy, total ethmoidectomy, resection of the maxillary sinus and right hard palate with local caspofungin instillation. During the following week, three additional endoscopic sinus surgeries were performed with resection of right concha media and palate combined with local AmBd administration. Histopathology of the resected tissue showed broad pauci-septate hyphae with right-angled branching and angioinvasion by hyphal elements (Fig. 2C) and the tissue culture was positive for *L. Corymbifera*. According to the susceptibility pattern, voriconazole was replaced with posaconazole.

Despite local and systemic antifungal treatment in combination with resection of infected areas in the pharynx and paranasal sinuses, MRI showed on day 17 progression of fungal infection with increasing inflammation in the nasopharynx, brain, cavernous sinus, right orbit and infarction extending the full length of the right optic nerve (Fig. 2D). Therefore, the patient underwent right-sided orbital exenteration, removal of the intracranial segment of the right optic nerve, debridement of involved structures in the middle cranial fossa and bilateral tonsillectomy. Additionally, an Ommaya reservoir was placed for intrathecal administration of AmBd. Histopathological examination of the removed eye revealed necrosis of the optic nerve head, inflammation of the retina and sclera end fungal spores in the sclera (Fig. 2E and F). An MRI angiography on day 25 revealed newly infarctions in the cerebellar hemispheres, vermis and occipital lobes, arteritis of the intracranial part of internal carotid artery and infected aneurysms in the inflamed cavernous sinus. Hemimaxillectomy was performed on day 27 and during the initial 48 days, the patient underwent 16 endoscopic sinus surgeries with local AmBd administration. Ophthalmological examination on day 46 revealed 1–2 mm ptosis, but otherwise normal conditions of the left eye. The patient underwent revision of necrotic bone in the orbital roof and reconstructive surgery of the right maxilla and orbit on day 53. Chemotherapy was resumed on day 69 and the patient is now in complete remission after 5.3 years of follow-up. Subsequent

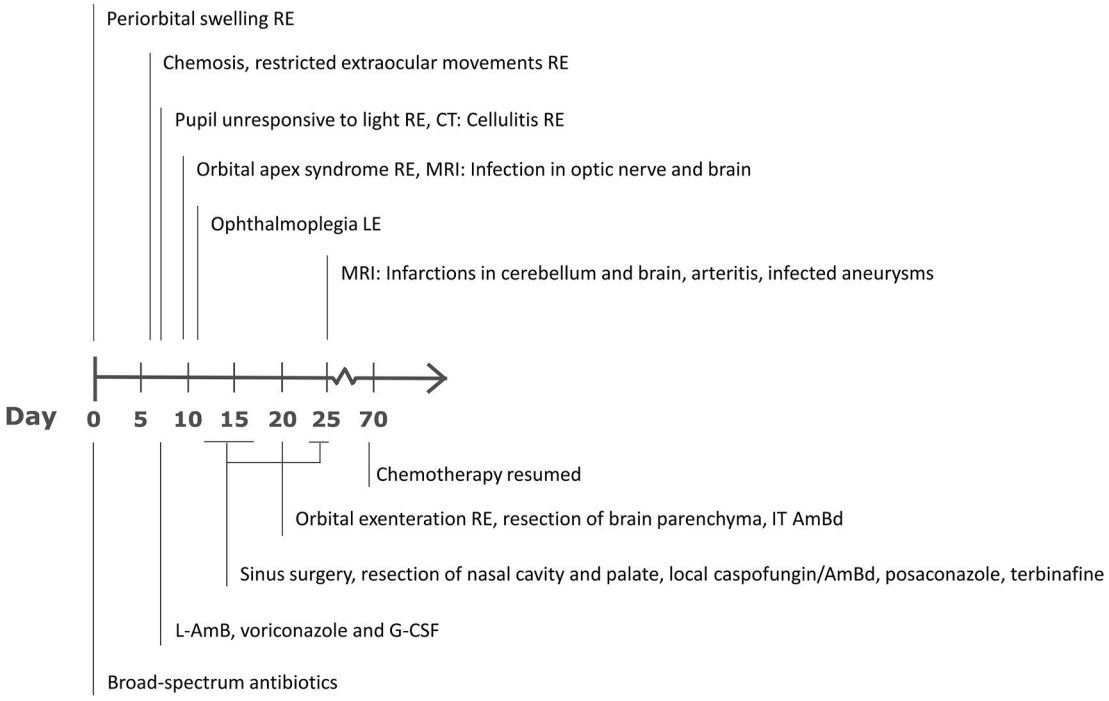

Fig. 1. Timeline of disease progression and treatment events in our patient with acute lymphoblastic leukemia and rhino-orbital-cerebral mucormycosis
Abbreviations: AmBd, amphotericin B deoxycholate; BE, both eyes; CT, computed tomography; G-CSF, granulocyte colony stimulating factor; IT, intrathecal; L-AmB, liposomal amphotericin B; LE, left eye; MRI, magnetic resonance imaging; RE, right eye.

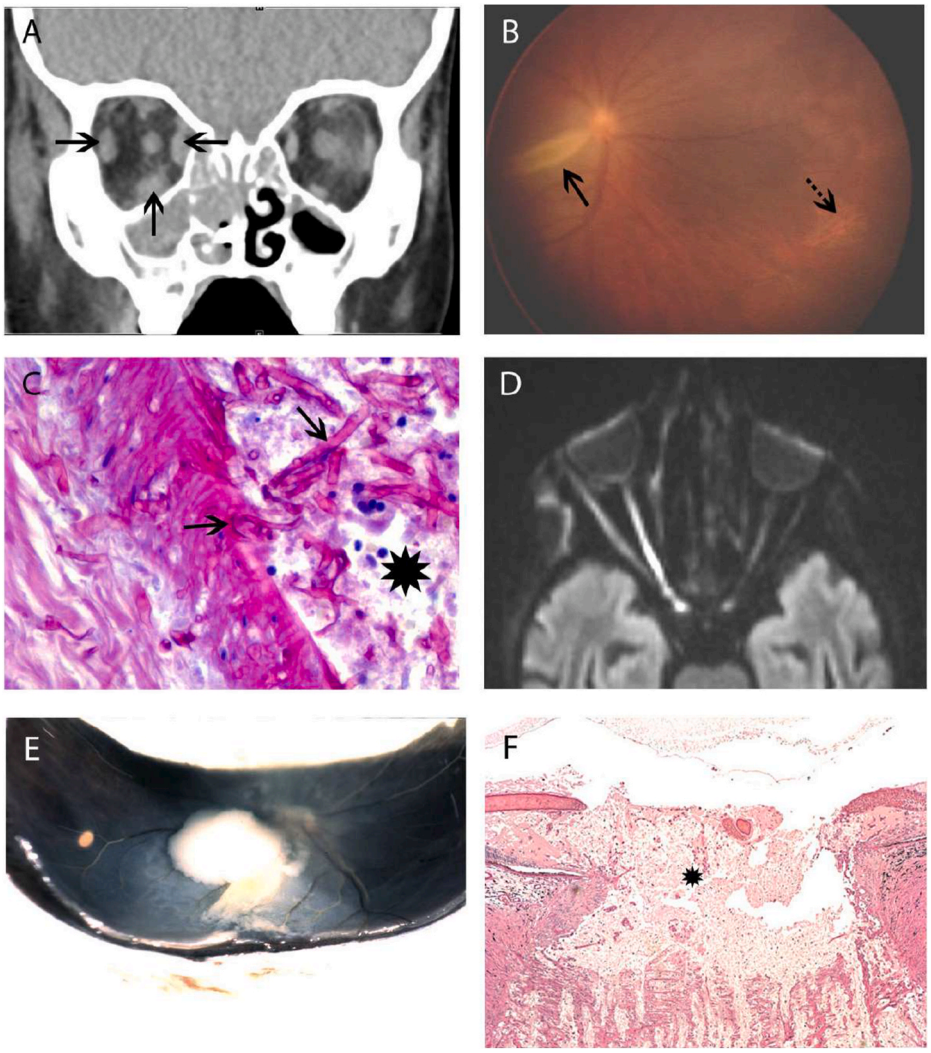

Fig. 2. Rhino-orbital-cerebral mucormycosis in a 3-year-old girl with acute lymphoblastic leukemia. (A) Coronal computed tomography scan showing opacification of the right maxillary sinus and ethmoidal cells and enlargement of the right inferior, lateral and medial rectus muscles (arrows). (B) Fundus photo of the right eye showing blurred disc margin, a creamy white infiltrate in the peripapillary area of the choroid (solid arrow) and a creamy white infiltrate in peripheral retina (dotted arrow). (C) Histopathological slide with PAS staining showing invasion of blood vessels and fungal hyphae. The lumen of the blood vessel (asterisk) and hyphae (solid arrows). (D) Diffusion-weighted magnetic resonance imaging scan showing infarction of the right optic nerve (white indicating infarction). (E) Fungal infiltrate of the retina of the resected right eye. (F) Histopathological slide with PAS staining of the optic nerve head (asterisk) showing necrosis, inflammation and fungal infiltration.

ophthalmological examinations have shown normal conditions of the left eye. The patient presently attends an ordinary primary school with no apparent intellectual deficit or reading problems.

2. Discussion

ROCM is a rare rapidly progressive life-threatening fungal infection occurring predominantly in immunocompromised and diabetic patients. Increased susceptibility is associated with neutropenia, exposure to broad-spectrum antibiotics, corticosteroids, uncontrolled hyperglycaemia and voriconazole prophylaxis. The latter due to intrinsic resistance.[6] In this case fluconazole was used as antifungal prophylaxis, but the patient received prolonged high-dose systemic corticosteroids as part of the induction therapy, had severe neutropenia and received broad-spectrum antibiotics before developing ROCM. The high mortality rate is due to delayed diagnosis and treatment failure. Diagnosis of mucormycosis generally remains very difficult. Initial clinical findings are mostly nonspecific and comprise headache, fever, rhinorrhea, sinusitis and mucosal necrosis. Progression of the infection to the orbit, optic nerve and ophthalmic vessels may lead to periorbital swelling and pain, chemosis, proptosis, ophthalmoplegia and loss of vision.[3,5] In our patient, progression of the periorbital swelling with hyperemia of the conjunctiva, chemosis and mildly restricted extraocular movements was interpreted as serous conjuncitivitis. A clinical diagnosis of fungal infection was made when the patient developed areactive mydriasis and a necrotic palatal lesion. However, in retrospect the chemosis and mild ophthalmoplegia have probably been due to mucormycosis-induced postseptal cellulitis and the delayed diagnosis has probably led to progression of the disease.

In ROCM, imaging usually provides nonspecific findings. CT scan may show mucosal thickening of the nasal cavity and paranasal sinuses, enhancement of soft tissue masses or bony destruction. MRI is more sensitive concerning intracerebral and intraorbital involvement, the latter characterized by thickening of the rectus muscles and inflammatory orbital fat changes, appearing hyperintense on T2-weighted images.[7] In contrast to Aspergillus infection, a serologic diagnosis of mucormycosis is hampered by the unavailability of serum diagnostic markers. Molecular tools have recently been developed to identify mucormycosis. Most commonly used methods are conventional PCRs, PCR-restriction fragment length polymorphism, DNA sequencing and real-time PCR. Although the efficiency of these assays has not been widely studied, they can be recommended as valuable add-on tools to complement conventional diagnostic procedures. Even in the presence of hematogenous dissemination of fungi, the fungus can rarely be cultured in blood and the detection of specific antibodies in patients with ROCM has shown low sensitivity and specificity.[8] Thus, early tissue biopsy and histologic identification of fungi remain the gold standard of diagnosis, as cultures of tissue samples are negative for the fungus in 40%. The typical histopathologic appearance of mucormycosis shows large, broad, nonseptate or pauci-septate hyphae with right-angle branching and vascular invasion with infarction,[9] as observed in our patient in whom diagnosis of ROCM was made by characteristic

histological features and by means of a positive tissue culture.

Our case adds to only a few surviving cases of ROCM arising in patients with ALL reported in the literature.[10] Optimal treatment of ROCM involves both reversal of predisposing conditions, early aggressive surgical debridement and appropriate antifungal therapy.[3] The local and systemic antifungal therapy of our patient has been described in detail previously.[11] An aggressive surgical strategy with repeated procedures to obtain local control has been associated with improved prognosis and survival rate.[4] The surgery in this case included resection of most of the midface of the right side including orbital exenteration, removal of the hard palate, the intracanalicular segment of the right optic nerve as well as fungal colonies in the middle cranial fossa. The surgery was extensive and multidisciplinary due to progression of the infection despite antifungal therapy. In retrospect, our patient would likely have benefited from earlier aggressive surgery.

In conclusion, ROCM is a life-threatening infection requiring multidisciplinary management with systemic antifungal therapy and aggressive surgical resection of involved tissue, even in myelosuppression. It is a disease with nonspecific initial clinical symptoms. For ophthalmologists, it should be considered when dealing with a case of orbital apex syndrome, chemosis, proptosis, periorbital or facial swelling or necrosis, with or without involvement of cranial nerves in immunocompromised or diabetic patients. Early diagnosis is of extreme importance for successful treatment and for patient survival.

Patient consent

The patient's parent consented to publication of the case in writing, as the child is minor.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare no conflict of interest.

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