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Survival from Rhino-Orbital-Cerebral Mucormycosis in SARS-CoV-2-Positive Diabetic Patients: Two Case Reports

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Keywords
Rhino-orbital-cerebral mucormycosis · Orbital apex syndrome · Amphotericin B · COVID-19 · Invasive fungal infection

Abstract
Introduction: Rhino-orbital-cerebral mucormycosis (ROCM) is a rare angioinvasive fungal infection known to be associated with high morbidity and over 50% mortality. ROCM is becoming more common due to an increase in predisposing immunocompromising comorbidities as well as COVID-19. ***Case Presentations:*** We report 2 cases – a 75-year-old woman with diabetes and a 39-year-old man with recurrent diabetic ketoacidosis. Both presented initially with acute sinonasal symptoms, were positive for SARS-CoV-2, and diagnosed with acute ROCM. Both underwent mutilating surgical therapy as well as high-dose amphotericin B treatment. With continued oral antifungal treatment, patient 1 showed stable symptoms despite radiographically increasing disease and died of urosepsis 5 months after first surgery. With posaconazole treatment, patient 2 recovered from the disease and showed no clinical sign of disease progression after 1 year. ***Conclusion:*** Despite the rarity of the disease, ROCM should be considered if the

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findings of clinical and radiological examination fit, so that a delay in treatment initiation can be avoided. As our both cases show, survival from ROCM is possible – albeit at a high cost.

Introduction

Rhino-orbital-cerebral mucormycosis (ROCM) is a rare and potentially deadly infectious disease caused by angioinvasive mold infection of the paranasal sinuses and the adjacent structures, such as the orbit, cavernous sinus, skull base and brain. Angioinvasion results in vascular obstruction and necrosis, leading to devastating local complications. Therapy includes surgical debridement and high-dose antifungal treatment as well as management of underlying risk factors. We present 2 cases of patients with ROCM treated at our hospital who survived the disease. Our aim was to highlight and discuss the clinical pictures, the imaging characteristics, diagnostics and therapy, as well as to give a long-term therapeutic management proposition in case of survival.

Case Presentation

Patient 1

A 75-year-old woman with poorly controlled diabetes was admitted to our tertiary care university hospital with progressing orbital apex syndrome, despite high-dose steroids, valacyclovir and ceftriaxone for several differential diagnoses. Magnetic resonance imaging (MRI) showed left optic nerve ischemia, severe orbital cellulitis, proptosis, and cavernous sinus thrombosis (Fig. 1). The left ethmoid air cells were partially destroyed ("empty nose sign," Fig. 1). Examination of blood serum and cerebrospinal fluid revealed no signs of an autoimmune-inflammatory, granulomatous, or infectious disease. Routine nasopharyngeal swab was positive for SARS-CoV-2. An ear, nose and throat specialist noted a brown crust on the basal turbinate. Vision in the left eye worsened. In the absence of a definitive diagnosis, the MRI of the head was repeated, revealing progression of the orbital findings, destruction of the left nasal cavity, progression of the cavernous sinus thrombosis, and irregularity of the internal carotid artery (ICA) indicative of secondary vasculitis. As ROCM as possible cause was discussed, endoscopic nasal surgery was performed as soon as possible. The left nasal cavity was now covered in black necrotic eschars (Fig. 2). Treatment with high-dose liposomal amphotericin B (10 mg/kg/d) was administered. Biopsy tissue showed ribbon-like, non-septate fungal hyphae, extensive necrotizing inflammation (Fig. 2), and angioinvasion. ROCM was confirmed by microbiological culture showing *Rhizopus arrhizus*. Extensive necrosectomy of the left nasal cavity and sinus with exenteration of the left orbit was performed (Fig. 3). The surgical treatment options were then considered to be exhausted and the patient's prognosis poor. She received home-care support, with continued posaconazole 5 × 100 mg. She was regularly seen for wound control and reported reduced general health but stable symptoms. A follow-up MRI 10 weeks later showed progressive ROCM involving the anterior skull base, the left masticator space, the optic chiasma and contralateral optic nerve, bilateral frontobasal, lepto- and pachymeningeal enhancement with edema in the adjacent gyri recti, and complete left ICA occlusion, without evidence of cerebral ischemia (Fig. 3). Seven weeks later, the patient died of urosepsis, severe anemia, and metabolic acidosis.

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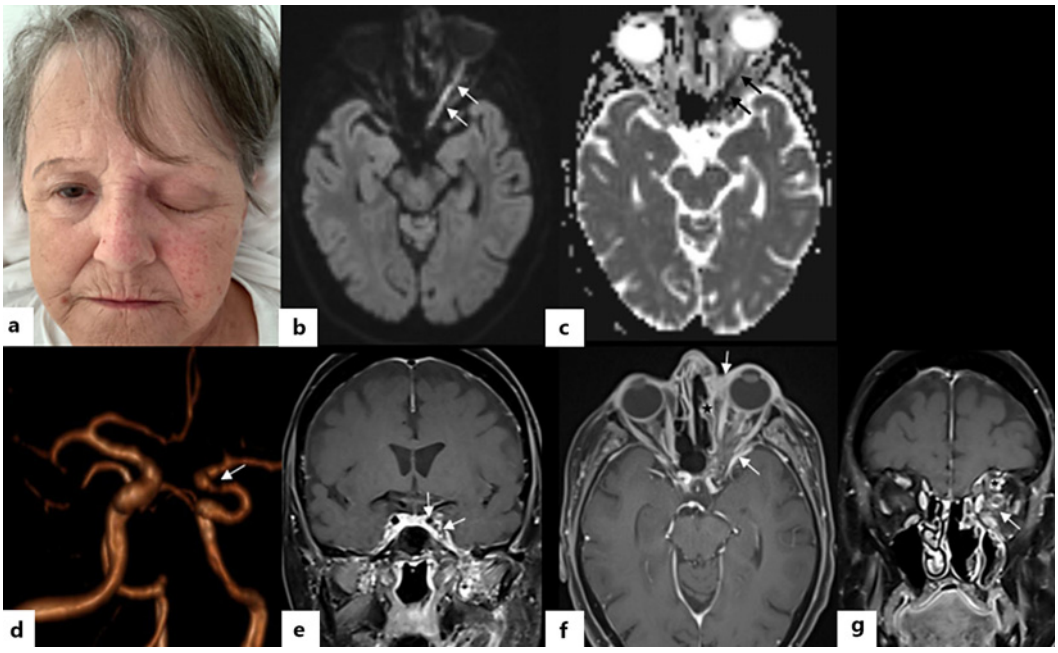

Fig. 1. Patient 1: initial clinical examination and initial in-house MR scan. **a** Clinical appearance at first examination at our hospital, presenting with left face and eyelid swelling, diffuse erythema, and ophthalmoplegia. DWI (**b**) with corresponding ADC (**c**) revealed diffusion restriction of left optic nerve (arrows) indicative of optic nerve ischemia. **d**. Reduced left internal carotid artery (ICA) caliber indicative of secondary vasculitis (compare white arrow in the 3D reconstruction of the 3D-time of flight angiography [3D-TOF MRA]). The T1-weighted coronal (**e**, **g**) and axial (**f**) starVIBE with fat saturation after administration of contrast showed the left cavernous sinus thrombosis with reduced flow void of the ICA (white arrows in **e**). The left extraocular muscles were edematous with enhancement (see arrow in **f** and black star in **g**) as with myositis. The left optic nerve showed significant enhancement (arrow in **g**). There was a frank osseous destruction of the left paranasal sinus with mucous retention in the anterior ethmoid (black star in F) and imaging appearance of an "empty nose" on the left side in side comparison (**f**, **g**).

Patient 2

A 39-year-old male Moldovan guest worker had been treated for severe diabetic ketoacidosis and right sinusitis with right facial pain and hypesthesia. A routine test for SARS-CoV-2 was positive. The ketoacidosis worsened, and he developed right exophthalmos and blindness. A follow-up MRI showed severe intraorbital cellulitis (Fig. 4). The patient was transferred to the intensive care unit of our tertiary care hospital for metabolic disturbance management. Examination by an ear, nose and throat specialist revealed severe right pansinusitis with black necrotic eschars suggestive of ROCM. Right orbital decompression and fronto-spheno-ethmoidectomy was performed (Fig. 5). Histopathological examination revealed nonseptate hyphae branching at 90° angles, with necrotizing inflammation and angioinvasion on hematoxylin and eosin and periodic acid-Schiff stained samples, compatible with mucormycosis (MM) (Fig. 5). Microbiological cultures showed evidence of *Rhizopus arrhizus*. Immediate treatment with high-dose liposomal amphotericin B (10 mg/kg/d) was initiated. The right orbit was exenterated; the skull base and the pterygopalatine fossa were debrided. MRI showed progression of the inflammation along the right trigeminal branches and into the right cavernous sinus with consecutive thrombosis, as well as pachymeningeal enhancement of the right temporal and frontobasal region (Fig. 6). Debridement of the right skull base and pterygopalatine fossa was performed. MRI revealed further progression to the

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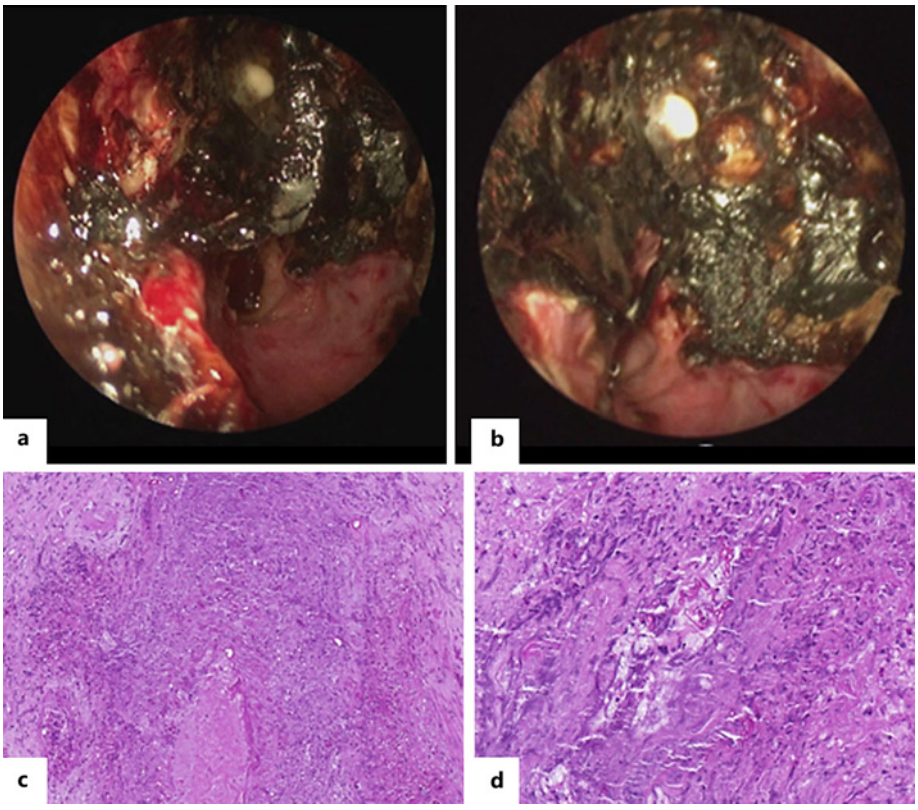

Fig. 2. Patient 1: intraoperative endoscopic intranasal view and histopathology. **a**, **b** Intraoperative endoscopic intranasal view of the necrotic eschars within the left nasal cavity. **c**, **d** Periodic acid-Schiff (PAS) stain (×40). Variable sized, ribbon-like, nonseptate fungal organisms, with 90-degree angle branching. Extensive purulent and necrotizing inflammation, compatible with Mucor partly located within blood vessels, leading to an image of occlusive vasculitis.

central and paracentral skull base with perineural spread. Complete removal of the infected tissue would have involved the cavernous sinus, which was considered impossible due to potentially fatal complications. With best medical support, he was transferred to Moldova. Since amphotericin B was unavailable, antifungal treatment was switched to isavuconazole until posaconazole was available. One year later, the patient is clinically stable, being almost symptom free with daily posaconazole, and after great financial sacrifices. He has been seeking insurance in Germany, which would allow him appropriate follow-up.

Discussion

Epidemiology and Pathogenesis

The incidence of opportunistic fungal infections, especially CNS infections, has risen in recent decades due to increases in comorbidities such as diabetes and drug-induced immunosuppression. Most CNS mycoses originate from inoculation of the skin, nasal mucosa, or lungs and penetrate the CNS continuously or via the hematogenous route. The most common CNS mycoses manifest as meningitis, abscesses, or granulomas. *Cryptococcus neoformans*, *Candida albicans*, and *Aspergillus* spp. are the most common pathogens [1].

According to the WHO, the incidence of MM varies between 0.005 and 1.7 per million worldwide, being highest in India. The worldwide mortality rate is 68% in disseminated

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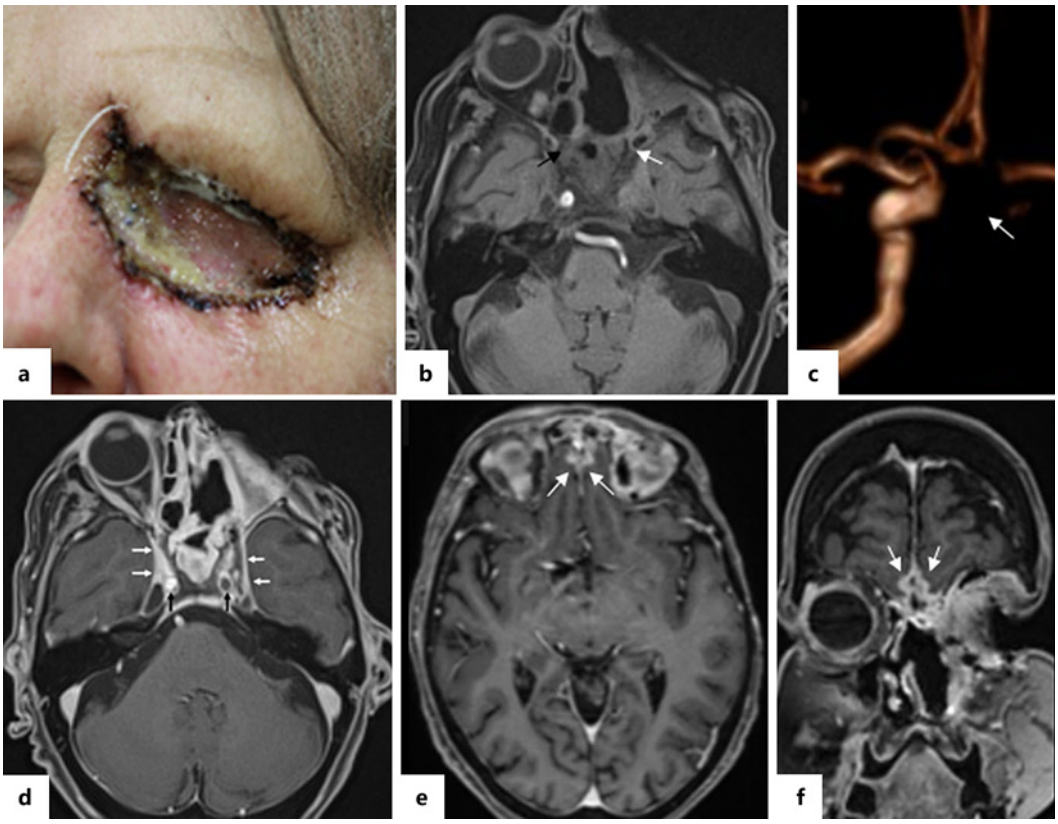

Fig. 3. Patient 1: postoperative clinical status and postoperative follow-up MRI after left orbital exenteration. **a** Clinical follow-up: situation after exenteration of the left orbital cavity. **b**, **c** The native axial T1-weighted starVIBE with fat saturation revealed a new filling defect of the left ICA (white arrow in **b**) in comparison to the normal flow void of the right ICA (black arrow in **c**). This was correlated in 3D-TOF MRA (arrow in C) confirming occlusion of the vessel. **e**, **f** The whole-brain post-contrast T1-weighted multiplanar reconstruction (MPR) (**e** axial and **f** coronal) showed perineural spread of the inflammation with extension and contrast enhancement of the frontobasal pachymeninx bilateral (arrows).

disease and 31% in cutaneous disease (data from the pre-COVID-19 era) [2]. MM is an angioinvasive infection caused by fungi of the order Mucorales, of which approximately 27 species are associated with human infections. *Rhizopus arrhizus* is the pathogen most commonly associated with MM, followed by species of *Lichtheimia*, *Apophysomyces*, *Rhizomucor*, *Mucor*, and *Cunninghamella* [3]. Sites of infection (in descending order) include the rhino-orbital-cerebral region, skin, gastrointestinal tract, and the lung and kidney, disseminated disease being the least common [2]. Transmission occurs through cutaneous or mucosal inoculation with environmentally ubiquitous spores [4]. They attach to the mucosa and proliferate into massive numbers of hyphae. Dead tissue and a hypoxic milieu are an optimal breeding ground to maintain the infection. Vessel invasion causes vasculitis and thrombotic occlusions leading to ischemia (pseudo-)aneurysm, and gangrene [5]. Risk factors include poorly controlled diabetes and diabetic ketoacidosis, immunosuppression, neutropenia, iron overload, steroid use, and HIV.

Rhino-Orbital-Cerebral Mucormycosis and COVID-19

A massive increase in the worldwide incidence of invasive fungal diseases was reported in patients with severe COVID-19 infection or convalescing afterward. In some regions of India, MM was declared an epidemic [2]. Immuno-dysregulating effects or endothelial

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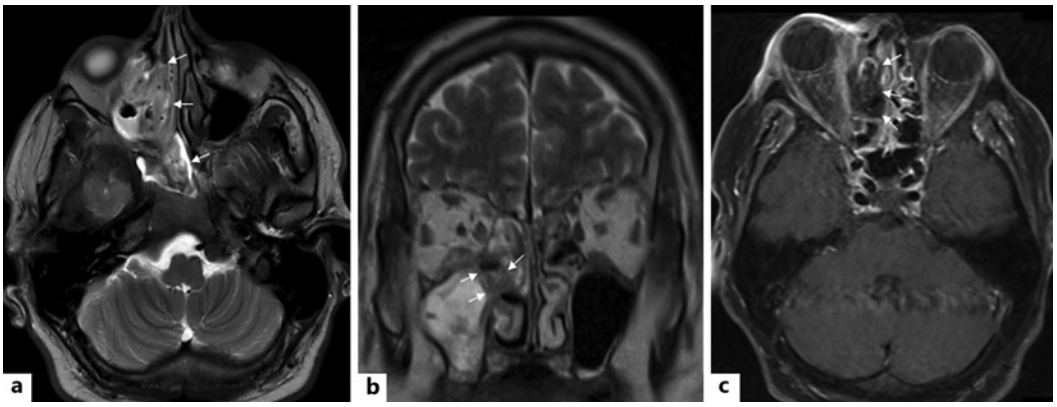

Fig. 4. Patient 2: initial clinical examination and initial in-house MR scan. Due to the patient's pronounced movement, the scan is slightly superimposed by artifacts. Axial (**a**) and coronal (**b**) T2-weighted (T2w) images revealed extensive hypointense mucoid retentions on the right paranasal sinus (white arrows) with complete obliteration of the maxillary, ethmoid, and sphenoid sinus. **c** These mucoid retentions are without enhancement on the T1-weighted (T1w) post-contrast phase (white arrows) thus demonstrating the "black turbinate sign" indicative of angioinvasive fungal sinusitis.

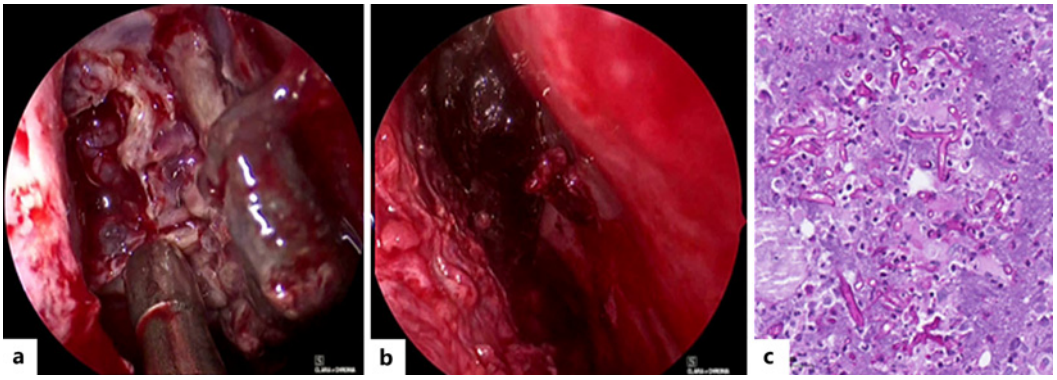

Fig. 5. Patient 2: intraoperative endoscopic intranasal view and histopathology. **a**, **b** Intraoperative endoscopic intranasal view of the necrotic eschars within the right nasal cavity. **c** Periodic acid-Schiff (PAS) stain (×40). Ribbon-like, nonseptate fungal organisms, with 90-degree angle branching. Extensive purulent and necrotizing inflammation compatible with Mucormycetes partly located within blood vessels, resulting in occlusive vasculitis.

dysfunction seems to play a role [6, 7]. Risk factors include severe and/or active COVID-19 infection, steroid administration, and male sex. Vaccination against COVID-19 seems to be protective [8]. In both our patients, COVID-19 was routinely tested for without evidence of active infection.

Diagnosis

Clinical Signs and Findings in ROCM

Clinical findings include discolored nasal discharge, congestion, facial swelling and pain, skin and mucosal necrosis, and signs of systemic infection as well as orbital symptoms (ophthalmoplegia, vision loss, proptosis). Altered mental status can occur [7, 9]. Black crusts

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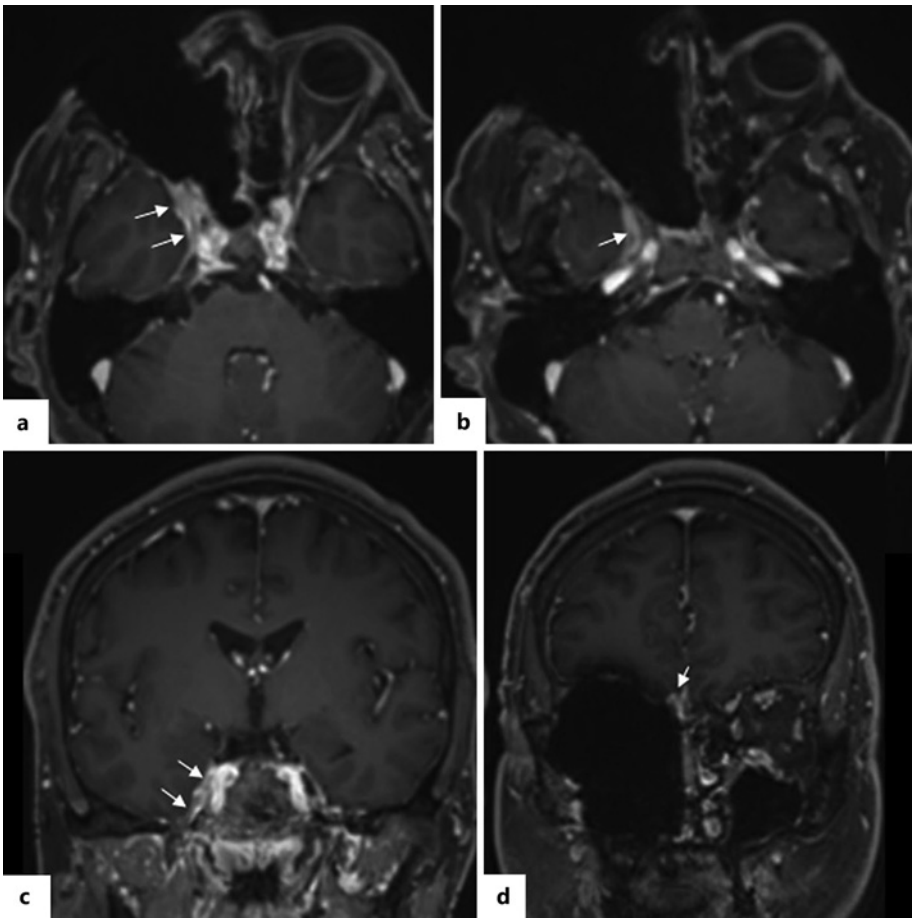

Fig. 6. Patient 2: postoperative follow-up MRI after left orbital exenteration. **a**, **b** The axial T1-weighted MPR post-contrast shows progression of the inflammation with progressive opacification of the right cavernous sinus (arrows). **c** The coronal T1-weighted MPR after contrast revealed a perineural extension along the course of the left mandibular nerve on the right side (arrows). **d** The coronal T1-weighted MPR after contrast shows an avid enhancement of the right frontobasal pachymeninx.

or necrotic mucosa can only be seen by nasal endoscopy. Symptoms evolve within days to weeks. Diagnosis of the rare chronic course of ROCM is more challenging due to nonspecific, slowly evolving symptoms. As early treatment is crucial for improving outcome, treatment often has to be initiated before positive laboratory or histopathological findings can confirm the diagnosis of ROCM.

Histopathology and Microbiology

Diagnosis is made based on microbiological cultures and microscopic evidence. The disease is characterized by ribbon-like nonseptate right-angled branching hyphae, 10–30 μm in diameter and 6–50 μm wide seen on specially stained samples (hematoxylin eosin, periodic acid-Schiff, Gomori Grocott's methenamine silver stain) [10]. Cultures are best grown from tissue samples rather than swabs [5]. Serum PCR for Mucorales DNA is not yet implemented in routine laboratory diagnostics. With a sensitivity of 85.2% and a specificity of 89.8%, it may be a promising and fast future diagnostic tool [11].

Imaging

A computed tomography scan of the paranasal sinus indicates bony destruction. However, MRI is the modality of choice for the diagnosis and staging of ROCM to determine extrasinus and intracranial disease extension [12]. A T2-weighted hyperintense signal with diffusion restriction and lack of contrast enhancement, known as the "black turbinate sign," is indicative of necrotic avital tissue. The middle turbinate is the most frequently affected site in the nasal cavity [9]. Extrasinus extension without initial bony destruction, due to ROCM's angioinvasive propensity and ability to disseminate along perivascular and perineural channels, is one of the imaging hallmarks. Therefore, the fat tissue, skull base foraminae and fossae, masticator space, palate, and oral cavity must be carefully examined. Early ROCM involvement is seen as a stranding of fat planes, inflammatory edema, and tiny abscess formations.

To determine the spectrum of orbital involvement, extraocular muscles, the extra- and intraconal fat, optic nerve, the globe, the orbital apex, and bony orbital walls must be evaluated [13]. Optic nerve infarction is seen as altered T1 and T2 signal intensity of the involved nerve with diffusion restriction, whereas accompanying optic neuritis appears as thickening and enhancement of the optic nerve sheath [14]. The spectrum of intracranial disease spread includes vascular, parenchymal, meningeal, bony involvement, and perineural spread.

Management

ROCM therapy requires a multimodal approach with correction of the comorbidities, timely surgical debridement, and antifungal treatment [4]. Debridement reduces the microbial load and disturbs the microenvironment that favors fungal growth. Resection reduces mortality by 49% but comes at the cost of high cosmetic and functional sacrifices [15]. Resection of cavernous sinus, ICA, skull base and even dura and brain tissue is technically possible [16], and certainly necessary for limiting the disease [7], but entail considerable perioperative risk and need to be discussed thoroughly. The therapy of choice is 5–10 mg/kg/day liposomal amphotericin B. Retrobulbar injection of amphotericin B can reduce infective activity within the orbit [17]. There is no satisfactory literature on the long-term management and treatment of ROCM survivors. Close clinical and radiological (MRI) follow-up enables determination of disease progression over time.

Orbital exenteration and skull base debridement were designated as the final surgical measure in both our patients. Both continued high-dose antifungal therapy (patient 1 with posaconazole, patient 2 with isavuconazole and later posaconazole) and were clinically stable. Case I had progressive radiological disease but no further clinical signs, and died of urosepsis. Case II recovered with daily antifungal treatment. Radiological follow-up and repeated biopsies are probably indicated to determine the course of the disease.

Conclusion

We treated 2 patients with ROCM who shared the risk factors of out of control diabetes and positivity for SARS-CoV-2. Case I had received steroids beforehand, and ROCM was diagnosed after some delay. Case II was diagnosed immediately. Both underwent mutilating therapy, exenteration of the orbit, and skull base debridement, which was the maximum reasonable surgical measure. High-dose amphotericin B was administered as soon as ROCM was suspected. Case I survived for several weeks with stable symptoms despite progressing radiological findings and then died of urosepsis, having been weakened by the disease. Case II has so far survived for over 1 year under long-term antifungal treatment. However, he remains

susceptible to disease recurrence and should have careful radiological and histopathological/microbiological follow-up.

Despite the rarity of the disease, ROCM should be considered if the findings of clinical and radiological examination fit, so that a delay in treatment initiation can be avoided. As both cases show, survival from ROCM is possible – albeit at a high cost. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000538539).

Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Both patients provided written general consent as well as an informed consent to participate in this study. Data requests may be sent to franca.wagner@insel.ch. General informed consent was provided for both patients.

Patient 1: written informed consent was obtained from the patient's next of kin for publication of the details of their medical case and any accompanying images. Patient 2: written informed consent was obtained from patient 2 for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Claudia Lädrach designed, drafted, revised, and approved the paper. Martin Wartenberg provided the histopathological images, acquired and analyzed data, and revised and approved the manuscript. Stefan Zimmerli, Julian Ebner, and Stefan Bohlen acquired and analyzed data and revised and approved the manuscript. Lukas Anschuetz acquired and analyzed data, provided the intraoperative images, and revised and approved the manuscript. Claire M.F. de Gouyon Matignon de Pontouraude and Marco Caversaccio revised and approved the manuscript.Franca Wagner designed, revised and approved the paper, and provided the MR images.All authors agree to be accountable for all aspects of the work.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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