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Successful Management of Rhino-Orbital-Cerebral Mucormycosis in a Child with Acute-on-Chronic Kidney Disease and Malnutrition

Case report and literature review

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Abstract

Mucormycosis is a very rare fungal infection in children. It is caused by opportunistic fungi, and mainly affects immunocompromised patients. Early diagnosis is very important for a good outcome. Successful management requires the reversal of the underlying predisposing risk factors, surgical debridement and prompt administration of active antifungal agents, with liposomal amphotericin B being the first line therapy. This case, to the best of the authors' knowledge, is the first rhino-orbital-cerebral mucormycosis to be reported on among Omani children. We highlight the importance of early diagnosis and prompt surgical and medical interventions in achieving a satisfactory outcome and we review the published literature in regard to the management.

Keywords: Mucormycosis; Sinusitis; Proptosis; Liposomal amphotericin B; Rhizopus; Posaconazole; Malnutrition.

Introduction

Mucormycosis is a very rare fungal infection in children. It is caused by opportunistic fungi, and mainly affects immunocompromised patients.[1] Early diagnosis is very important for a good outcome.[2] Successful management requires the reversal of the underlying predisposing risk

factors, surgical debridement and prompt administration of active antifungal agents, with liposomal amphotericin B being the first line therapy.[3,4] This case, to the best of the authors' knowledge, is the first rhino-orbital-cerebral mucormycosis to be reported on among Omani children. We highlight the importance of early diagnosis and prompt surgical and medical interventions in achieving a satisfactory outcome and we review the published literature in regard to the management.

Case Report

We present a six-year-old Omani girl who was referred to a tertiary care hospital in Oman from a local health centre in 2016 with sudden onset facial swelling, left periorbital skin rash and reduced oral intake for one day. She had no history of fever, nasal congestion, ear pain or toothache. There was no history of allergy, preceding trauma or insect bites. She was not a diabetic and had no history of haematological malignancy or recurrent infections. She was operated on for meningomyelocele in the neonatal period. That was complicated by reflux nephropathy, chronic kidney disease and paraplegia. She had normal speech, vision and hearing.

The patient was very thin and weighed just 9 kilograms. She was tachypneic with acidotic breathing and she had a respiratory rate of 40 per minute, a pulse rate of 120 beats per minutes, and Blood pressure (BP) of 100/80 mmHg, Spo2 of 100% with 10 L of O2 via non-rebreathing mask. She had mild proptosis of the left eye, left sided facial swelling of the left orbit with multiple pustular lesions on the left eye brow, left side of forehead and nasal bridge **(Figure 1)**. She was not able to see from her left eye, but she had a normal ocular motility and fundus. An oral cavity examination showed multiple dental caries. Her left palatal mucosa was coated by a very thick white lesion opposite her upper first and second left molars, measuring 2x2 cm and with central dark discoloration **(Figure 2-A)**. Neurologically, she was conscious and oriented. She was hypotonic in both upper and lower limbs with brisk reflexes (her baseline). Other systemic examinations were unremarkable.

An initial laboratory investigation showed a haemoglobin of 6.84 g/dl, a white blood cell count of 38.8 X 10^3 with mainly neutrophils (35.35 X 10^3) and platelets count of 1078.00 X 10^3. Her C-reactive protein was very high (342 mg/L). Her venous blood gas showed metabolic acidosis with bicarbonate of 7.8 nmol/L and base excess of -22 mmol/L. She had acute-on-chronic kidney disease. Her urea was 22.6 mmol/L, her creatinine was 150.66 umol/L, while other electrolytes

were within normal limits. Her random blood glucose was 6.27 mmol/L and glycosylated HB (%HBA1C) was 4.42%. Her chest radiograph was normal.

She was initially admitted into the general paediatric ward and a diagnosis of periorbital cellulitis was made. A few hours later, she was shifted to a paediatric intensive care unit after she developed hypotension (BP: 48/40 mm Hg), which was corrected by two boluses of normal saline. A bicarbonate infusion was also given to correct her metabolic acidosis. She was given cefotaxime, amikacin, metronidazole and cloxacillin intravenously. Contrasted Computed topography (CT) of the orbits and brain revealed pan maxillary and ethmoid sinusitis (more on the left side) with subtle rarefaction of the left lamina paprychea. There was an inflammatory phelgmon of the medial and inferior wall of the left orbit measuring 28 x 7 mm. There was no evidence of bone destruction or intracranial involvement. **(Figure 3)**. Multidisciplinary teams (MDTs) were consulted urgently, including paediatric infectious diseases, ophthalmology, Oral Maxillofacial surgery (OMFS) and Ear, Nose and Throat (ENT) teams. The antimicrobial regimen was changed to renal-adjusted doses of intravenous ceftazidime, clindamicin and ciprofloxacin to cover the most likely causative organisms, including staphylococcus aureus, anaerobes and pseudomonas aeruginosa. In addition, an invasive fungal infection, such as mucormycosis was strongly suspected. Therefore, a diagnostic nasal endoscopy was performed within 24 hours of her being admitted, which showed necrosis of the left maxillary wall and upper part of the left inferior turbinate. Urgent KOH staining of the biopsy specimen showed aseptated cylindrical fungal hyphae. Subsequently, liposomal amphotericin B was administered empirically at a dose of 5 mg/kg/dose, once daily within 48 hours of admission. The histopathology showed necrotic tissue containing aseptated, broad fungal hyphae, displaying right angled branching with angio-invasion and thrombosis of the blood vessels, highly suggestive of mucormycosis **(Figure 4)**. The culture of the initial swab confirmed the growth of *Rhizopus spp.*

The patient underwent a debridement of the left nasal cavity, an inferior turbinectomy, medial maxillectomy and ethmoidotomy. Unfortunately, she developed skin necrosis in the medial aspect of the left eye two days after the operation. Intraorally, the left palatal region had the appearance of decreased vitality and bone necrosis was suspected. Repeated CT demonstrated that the left orbital phlegmon had extended up to the orbital apex, transformed into an abscess and increased in size to 31 x 10 mm. The optic nerve had thickened. However, there was no

intracranial abnormal enhancement and dural sinuses were normal. A left orbital exenteration was discussed, but the parents were reluctant to give consent. She underwent left palatectomy, maxillectomy and debridement on the 10th day after her admission. There was no drainable pus from the orbital abscess site. Despite this, she still had left orbital proptosis and increasing periorbital ecchymosis one week after the second operation. Therefore, magnetic resonance imaging (MRI) with contrast was done to further delineate the anatomy and extension. That showed left ethmoid opacification, abnormal enhancement of the left septal/preseptal area with extension to retro-orbital space and a small abscess formation in the left orbit, measuring 1.9 x 0.8 cm with mass effect causing optic nerve deviation and proptosis. It also revealed abnormal enhancement of the cavernous sinus, but no brain parenchyma extension. Lumbar puncture could not be done because she was not stable enough for the procedure. The addition of oral posaconazole was planned but she was not able to tolerate it orally. Instead, caspofungin was added to ambisome on 17th day of admission due to an un-satisfactory response and ceftriaxone was commenced to cover any secondary bacterial central nervous system infection. Furthermore, ethmoid sinus debridement was done and her left orbitotomy did not reveal any pus.

Only after her third operation did the clinical signs start to gradually improve. She started to see a little from her left eye and was able to count fingers with difficulty. But there was no further improvement as the disease progressed. Trans-orally, her inferior maxillectomy site was healing well with good re-epithelialsation. She was able to take some medicine and food orally after using a resin obturator to cover the post-operative palatal defect. Eventually, the histopathology from the third operation did not show any fungal elements and the culture was negative. Twenty-four days after admission, her creatinine started to improve to 104 umol/L after a period of fluctuation. Subsequently, her ambisome dose was gradually increased to 9 mg/kg/day. She was screened for immunodeficiency: she was not lymphopenic, her HIV serology was non-reactive, immunoglobulin levels and lymphocyte subset were normal. An ultrasound of her abdomen did not reveal any abscesses. After 8 weeks of ambisome and 4 weeks of caspofungin, she was discharged home and her therapy was transitioned to oral posaconazole at a dose of 17mg/kg/day in 3 divided doses. That was continued for 3 months whereupon a follow up- MRI showed a complete resolution of the abscesses in the left orbital region and left maxillary sinus. She was followed up regularly in the clinics by a multidisciplinary team. All her clinical signs improved with no relapse of infection to date **(Figure 2-B)**. The mother has given written consent to publish this case and its related images.

Discussion

Mucormycosis is a rare, aggressive, angio-invasive and highly destructive fungal infection with very high morbidity and mortality.[1,2,4] It is caused by ubiquitous fungi, predominantly belonging to the order Mucorales.[5] The *Rhizopus* species, the causative agent in our patient, is responsible for about one third of mucormycosis cases overall and accounts for 85% of rhino-cerebral cases.[2,6,7] The most important predisposing factors for mucormycosis are malignancies and poorly controlled diabetes mellitus.[1-9] Other predisposing factors include chronic kidney disease and malnutrition,[1] both of which were present in our patient. Recently, increasing mucormycosis cases were also identified worldwide in people with Coronavirus disease 2019 (COVID-19), particularly more in those with pre-existing diabetes mellitus and corticosteroids use.[8]

Rhino-cerebral mucormycosis has been associated with acute and chronic kidney disease with fatal outcome. Altered immune status, leucopenia and metabolic acidosis in those patients may be a plausible mechanism of predisposition.[10] As a risk factor, malnourishment in children is mainly associated with gastrointestinal mucormycosis.[1] There was no clinical or radiological evidence of abdominal organ involvement in our patient. In addition, her investigations were negative for diabetes mellitus and immunodeficiency.

The successful management of mucormycosis requires early diagnosis, reversal of underlying predisposing risk factors, prompt administration of active antifungal agents and aggressive surgical debridement.[3,4] Due to a lack of awareness of risk factors and nonspecific clinical and radiologic findings, many cases are not diagnosed for many weeks after the time of presentation.[3,4] Histopathology and fungal culture are considered the gold standard for the diagnosis.[4,7,11] Mucorales are readily recognized morphologically on the basis of non-septate or occasionally pauci-septate, broad, thin walled hyphae with wide angled branching and evidence of angioinvasion.[3,9,11] We believe that the early diagnosis achieved within 24 hours of patient's admission played a very important role in her satisfactory outcome.

Mucorales are resistant to most antifungals, except amphotericin B(AMB)–deoxycholate (including lipid formulations of AMB, ambisome) and the new triazole posaconazole.[5] While liposomal amphotericin B is the recommended first line therapy, posaconazole is mainly used as a stepdown or salvage therapy.[3,4,11,12] Chamilos et al showed that delayed amphotericin B therapy

(>= 6 days after diagnosis) was associated with a two-fold increase in mortality in patients with hematological malignancy and mucormycosis compared with early treatment (83% vs. 49%).[5] Ray et al reported a case of rhino-orbital mucormycosis in a child with acute kidney injury. Amphotericin B was started two weeks after admission. Although some clinical response was noticed, the child died of massive gastrointestinal hemorrhage.[10] The response rate to liposomal amphotericin B ranges between 23 to 58%.[12] The optimal dose is not known, but most experts recommend a daily dose of 5-7.5 mg/kg/day. Although higher doses can lead to nephrotoxicity, doses up to 10 mg/kg/day are recommended for disseminated diseases and are well-tolerated in children.[4,6,10,13]

On the contrary, the use of amphotericin B-deoxycholate is limited by its substantial nephrotoxicity, specifically in the doses and treatment duration needed for mucormycosis.[9] liposomal amphotericin B was commenced on our patient within 48 hours of admission. She tolerated increasing the dose to 9 mg/kg/dose once daily without worsening her renal parameters. Posaconazole has an overall success rate of 60–70% when used as a salvage agent.[14] A dose between 17 and 24 mg/kg/day is suggested in order to achieve target plasma concentration.[15] The addition of oral posaconazole as a salvage therapy was postponed in our case till the day of discharge because she was not able to tolerate it after the operation. Despite the late administration, our patient showed a good response to it on follow up. Echinocandins are not recommended because they have a modest effect against Mucorales in vivo and virtually no activity in vitro.[10,16] However, some reports suggested its use based on the the theory that *Rhizopus oryzae*, expresses the target enzyme for echinocandins (1,3-b-glucan synthase). In a small retrospective study, Caitlin et al reported a superior success rate in patients with rhino-orbital-cerebral mucormycosis who received polyene-caspofungin therapy compared to patients treated with polyene monotherapy.[15] Caspofungin was added to our case because of the progressive disease whilst on liposomal amphotericin B therapy and an inability to tolerate oral posaconazole initially.

Interestingly, she started to improve after the third operation, which coincided with initiation of caspofungin. Stronger evidence is needed, however, before recommending this agent for the treatment of mucormycosis.[9] Our patient received antifungal therapy for approximately 5 months. The reported length of treatment ranged between 3-36 months. This should be guided by the clinical and radiological response.[6,9]

De-bulking the infection by early aggressive surgical debridement is very important and critical component of therapy. Multiple surgeries may be required in the case of extensive disease.[11] Pana et al has demonstrated less mortality in those patient given combined antifungals and surgery compared to those given antifungals alone (18.5% versus 60%).[17] Our patient required 3 sessions of complex operations, without which, it was clear that pharmaceutical interventions were not sufficient to control the infection.

Conclusions

We described the successful management of severe rhino-orbital-cerebral mucormycosis in an Omani child. Despite a very high mortality reported, early diagnosis and prompt medical and surgical interventions were the key factors in achieving a good outcome in this case. Keeping a high index of suspicion and raising the awareness about this aggressive infection and its predisposing factors among all clinicians dealing with immunocompromised paediatric patients, is of paramount importance for early recognition and prompt management.

Authors' contribution

MAR is the first author who prepared, wrote, and reviewed the manuscript. TAM, AAA and VM contributed to writing and reviewing the manuscript. All authors read and approved the final manuscript.

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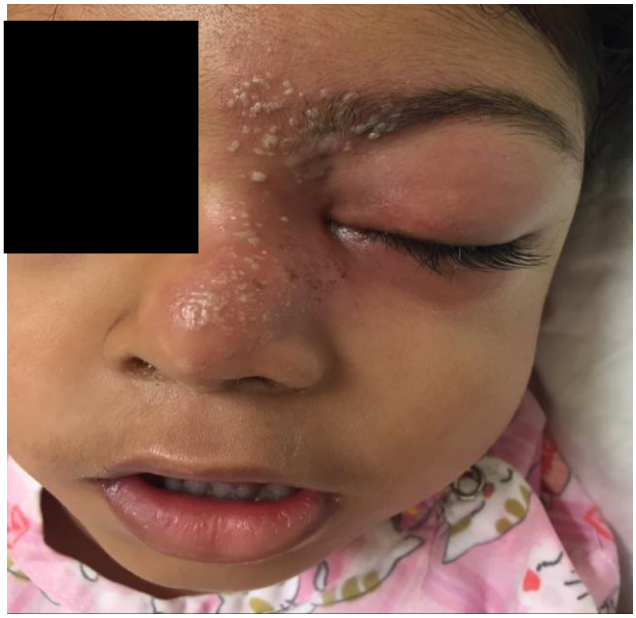

Figure 1: An image showing mild proptosis, swelling and redness of the left eye and multiple pustular lesions on the left eyebrow, left side of the forehead and nasal bridge.

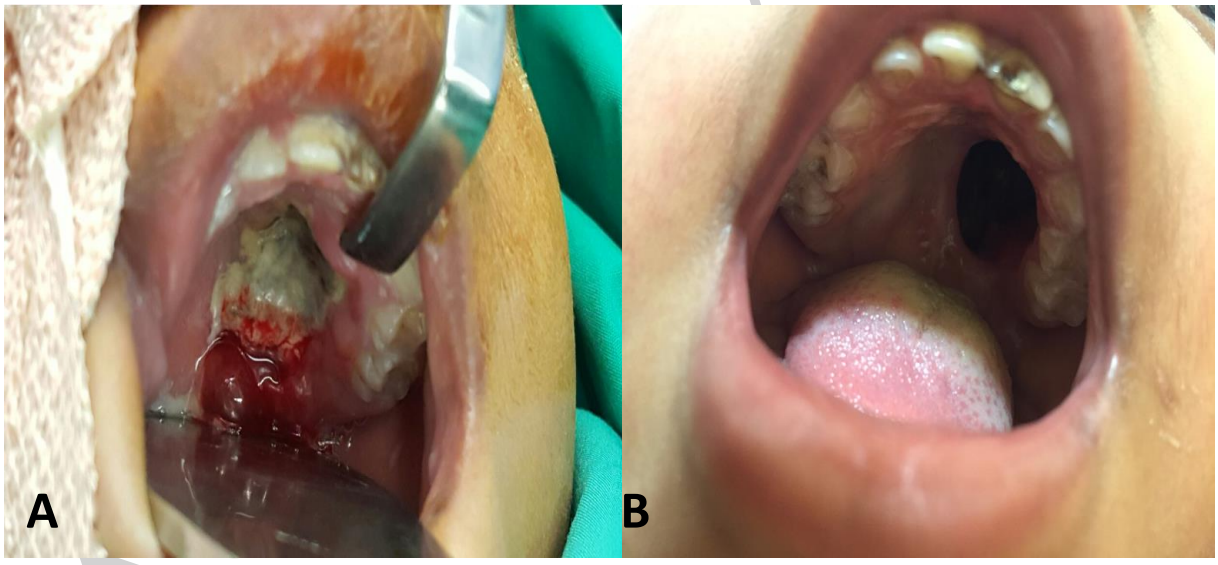

Figure 2: (A) An image showing very thick white lesion coating the hard palate with central dark discoloration, measuring 2x2 cm. **(B)** The oral cavity on follow up showing healthy and clear margin of the lesion.

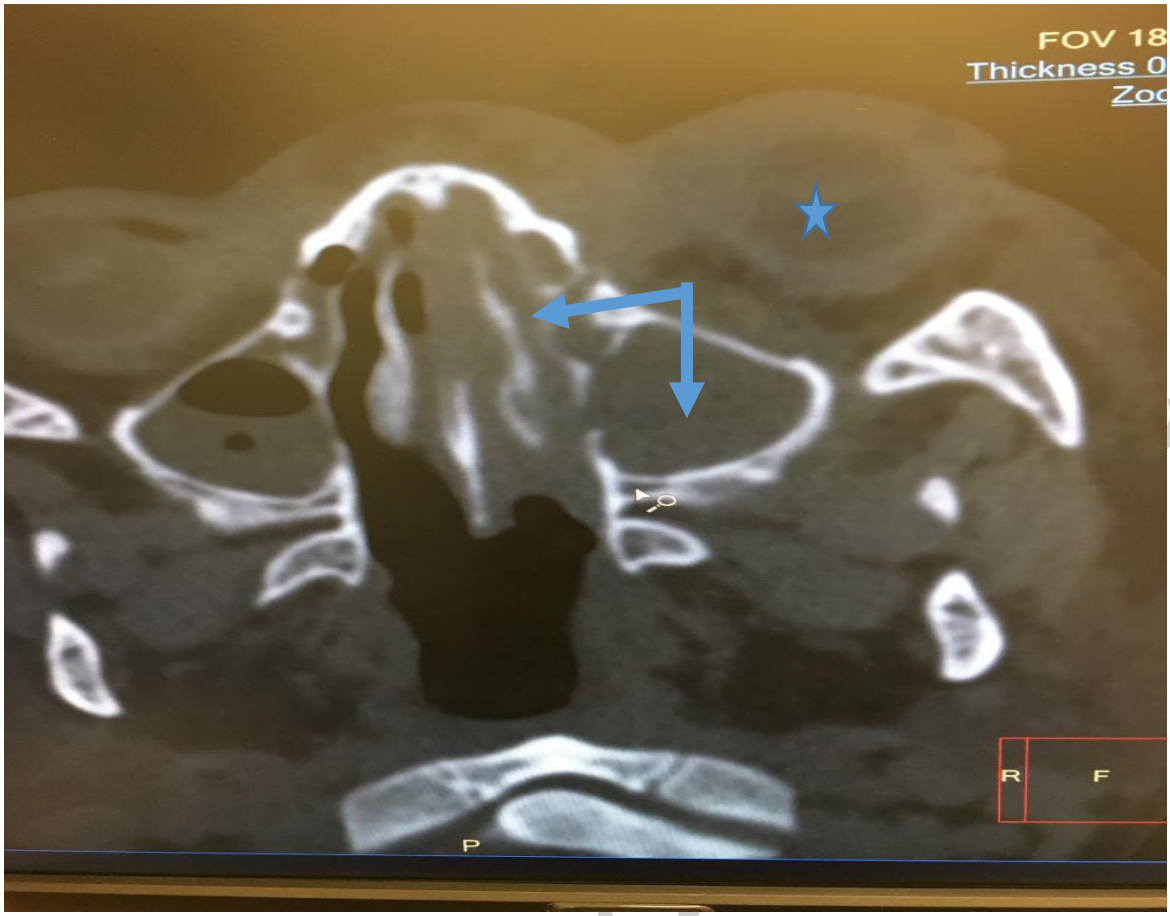

Figure 3: Axial CT orbit showing left eye proptosis (star), maxillary and ethmoid sinusitis (arrows) with subtle rarefaction of the left lamina paprychea.

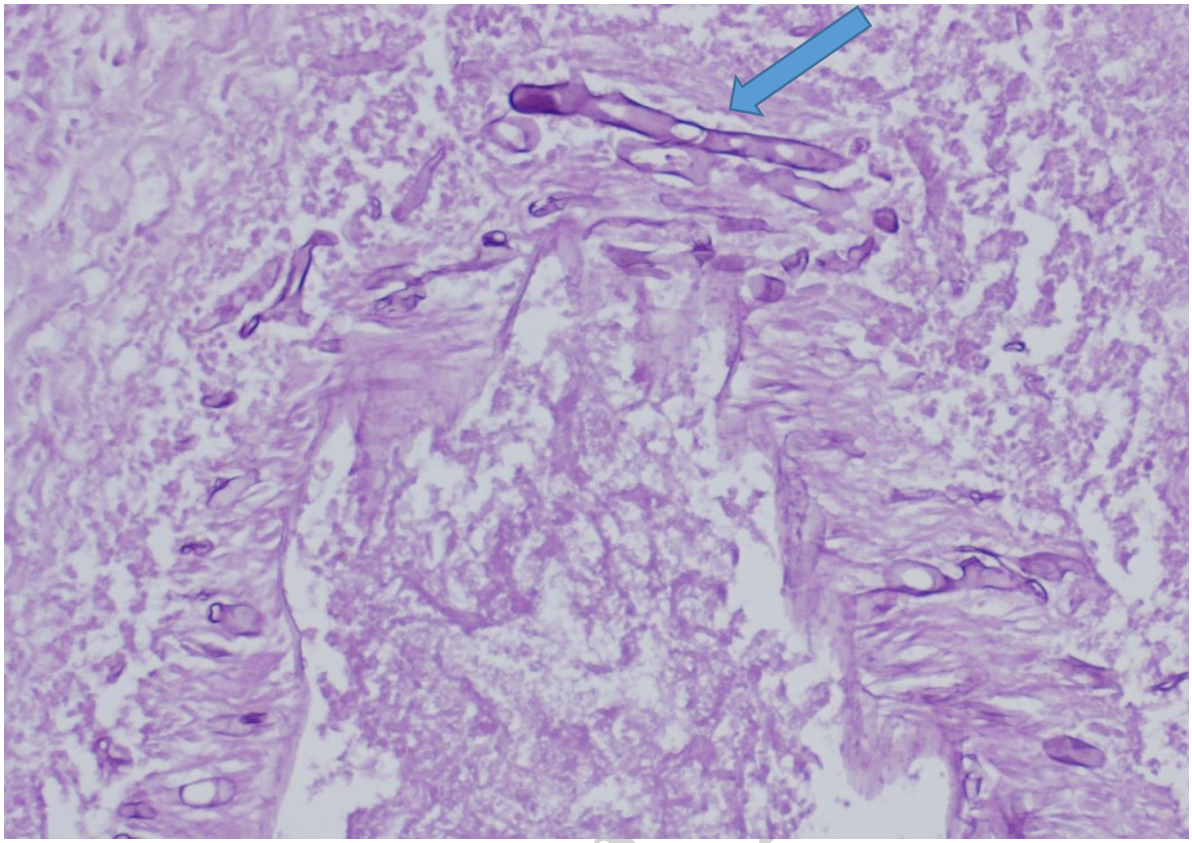

Figure 4: Section of nasal biopsy showing blood vessel invasion by PAS positive non-septate, broad, ribbon-like fungal hyphae (arrow), (PAS 200X).