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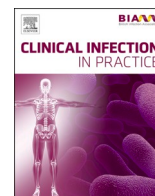


Image challenge: A diabetic man with facial swelling following recent Covid-19 infection

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ABSTRACT

A 68-year-old man with diabetes presented with shortness of breath, left sided facial swelling, and nasal discharge. He had recently returned from India and PCR was positive for SARS-CoV-2 Delta variant. CT head and diffusion-weighted MRI sinuses were performed and the patient underwent endoscopic sinus surgery before being transferred to a specialist skull base centre.

History

A 68-year-old man of Indian origin presented with a 3-day history of shortness of breath and headache after returning from Punjab, India. His past medical history included poorly controlled Type 2 diabetes (HbA1c on admission 139 mmol/mol, reference range 20–41 mmol/mol), chronic kidney disease, previous pulmonary tuberculosis, possible lung cancer that was still under investigation, and a tooth extraction a month ago in India. He had tested negative for COVID-19 prior to leaving India.

On presentation, he had a heart rate of 128, respiratory rate of 34, blood pressure of 142/106, oxygen saturations 90% on 4L oxygen, and he was afebrile. He was in diabetic ketoacidosis with blood glucose of 40 mmol/L, ketones of 7 mmol/L, and pH 7.22. Initial investigations showed raised inflammatory markers (CRP 124.6 mg/L, reference range 0–5 mg/L; WBC $14.5 \times 10^9/L$, reference range $4.2\text{--}10.6 \times 10^9/L$; neutrophils $13.1 \times 10^9/L$, reference range $2.0\text{--}7.1 \times 10^9/L$; lymphocytes $0.6 \times 10^9/L$, reference range $1.1\text{--}3.6 \times 10^9/L$), acute kidney injury (urea 15.9 mmol/L, reference range 2.5–7.8 mmol/L, creatinine 144 $\mu\text{mol/L}$, reference range 60–125 $\mu\text{mol/L}$), raised D-dimer (7223 ng/mL FEU, reference range 0–275 ng/mL FEU), and bilateral infiltrates on the chest radiograph. He tested positive for SARS-CoV-2 Delta variant on the day of admission and was transferred to the high-dependency unit where he

received dexamethasone, remdesivir, tocilizumab, and supplementary oxygen up to 60% FiO₂. CT pulmonary angiography showed changes consistent with COVID-19 and a right pulmonary embolism, for which he was anticoagulated.

On further questioning, he revealed a history of left sided facial swelling and left mucoid nasal discharge for approximately one month after his tooth extraction. On examination, there was swelling in the left maxillary area that was mildly tender, with no evidence of cellulitis, fluctuation or collection. There was mild swelling of the left eyelid, but it was painless with normal eye movements, acuity and pupillary reflexes. There was an upper left 6th tooth extraction in the mouth with no palatal lesions. On flexible nasoendoscopy, there was evidence of left sided congestion, mucus discharge and septal deviation to the left. Superficial nasal swabs were taken and sent for bacterial and fungal culture.

Initial CT head with contrast showed opacification of the maxillary antra, left ethmoid air cells, frontal sinuses, and sphenoid sinuses (Fig. 1). Following empirical therapy, he underwent endoscopic sinus surgery on day 14 involving left sided maxillary antrostomy, anterior and posterior ethmoidectomy, sphenoidotomy, and excision of the inferior turbinate (Fig. 2).

What is the most likely diagnosis from the history, radiology, and intra-operative findings?

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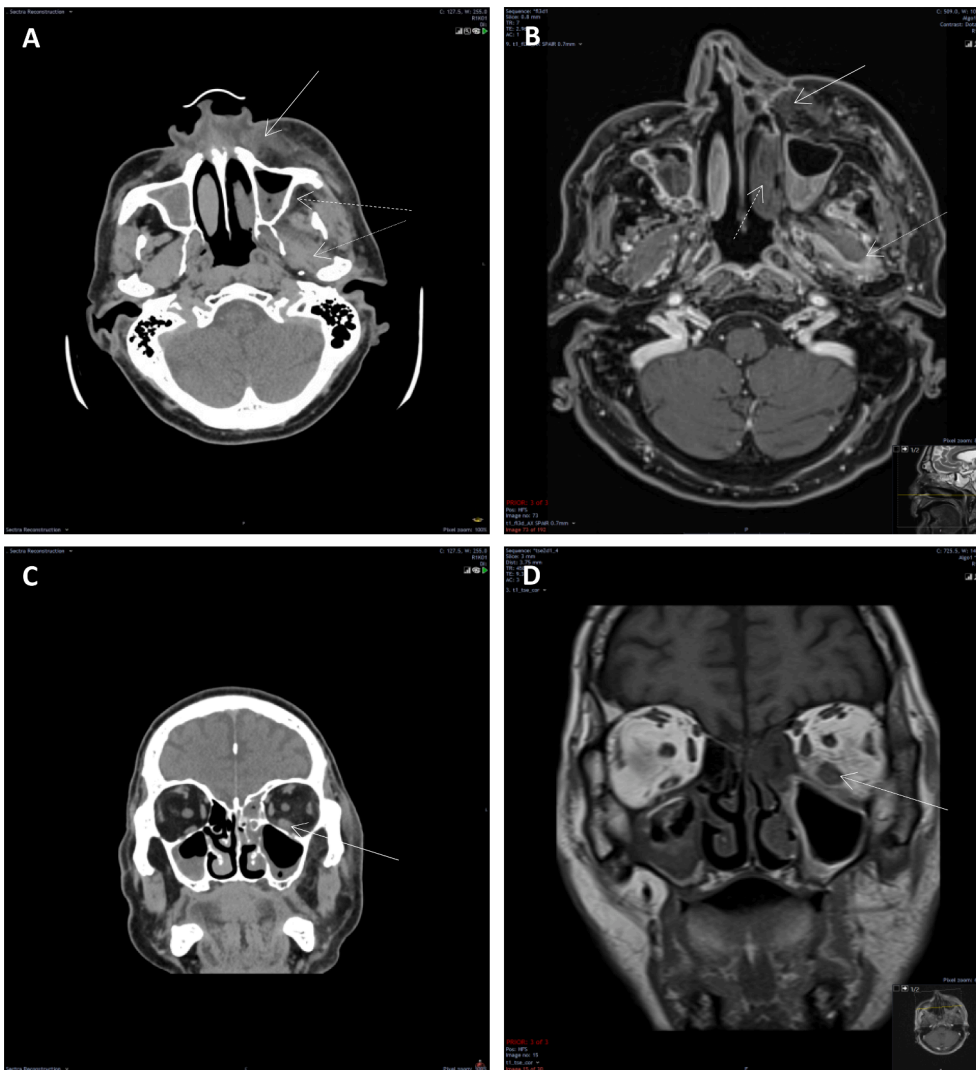


Fig. 1. CT and MRI at presentation. (A) Initial axial CT head demonstrating asymmetric soft tissue tracking over the left malar soft tissues inferior to the orbit (solid arrow), asymmetric fat stranding within the left retro-maxillary fat (dashed arrow), and asymmetric oedema of the left lateral pterygoid muscle (dotted arrow). (B) Initial MRI neck (post contrast fat saturated T1 axial sequence) demonstrating asymmetric hypo enhancing left malar soft tissue (solid arrow), asymmetric abnormally enhancing left lateral masticator space with mild hypo enhancing lateral pterygoid muscle (dotted arrow), and hypo enhancing left inferior turbinate (dashed arrow). (C) Initial coronal CT head and (D) coronal T1 MRI, demonstrating asymmetric oedema of the left inferior rectus muscle and adjacent orbital fat stranding (solid arrows).

How would you manage this patient?

Image challenge

Image challenge answers

Diagnosis

Given his recent travel to India, COVID-19 infection, and background of uncontrolled diabetes, mucormycosis infection was suspected. The diagnosis was confirmed on histology from the surgery, which showed fungal hyphae consistent with both *Mucor* and *Aspergillus spp* (Fig. 3), and superficial nasal swab cultures also grew *Rhizopus* species and *Aspergillus flavus*.

Management

Prior to surgery, he was empirically commenced on systemic liposomal amphotericin B (5 mg/kg) on day 6, as well as betamethasone 0.1% and xylometazoline 0.1% nasal drops and saline nasal douches.

The patient was transferred to our specialist infectious diseases unit on day 9.

Due to the extent of disease following surgery, amphotericin B was increased to 7 mg/kg and posaconazole 300 mg was added. This was subsequently switched to isavuconazole 200 mg, as the minimum inhibitory concentration of *R. microsporus* was 0.5 mg/L (sensitive) to amphotericin, 1 mg/L (sensitive) to isavuconazole, and 1 mg/L (intermediate) to posaconazole.

Outcome

Despite surgery and antifungal therapy his condition continued to progress. He developed chemosis, proptosis and complex ophthalmoplegia in the left eye and necrotic lesions in the upper hard palate. He also developed episodes of epistaxis, haemoptysis and melaena. Repeat MRI orbit and head with contrast on day 23 and CT skull base fine cut on day 24 showed progression of disease in the posterior soft tissues and orbital contents, bony erosive changes of the medial orbital wall, sphenoid septum and sphenoid posterior wall, and asymmetrical cortical erosion of the floor of the left middle cranial fossa and abnormal clivus marrow signal (Figs. 4 and 5). CT venogram showed no cerebral venous system involvement.

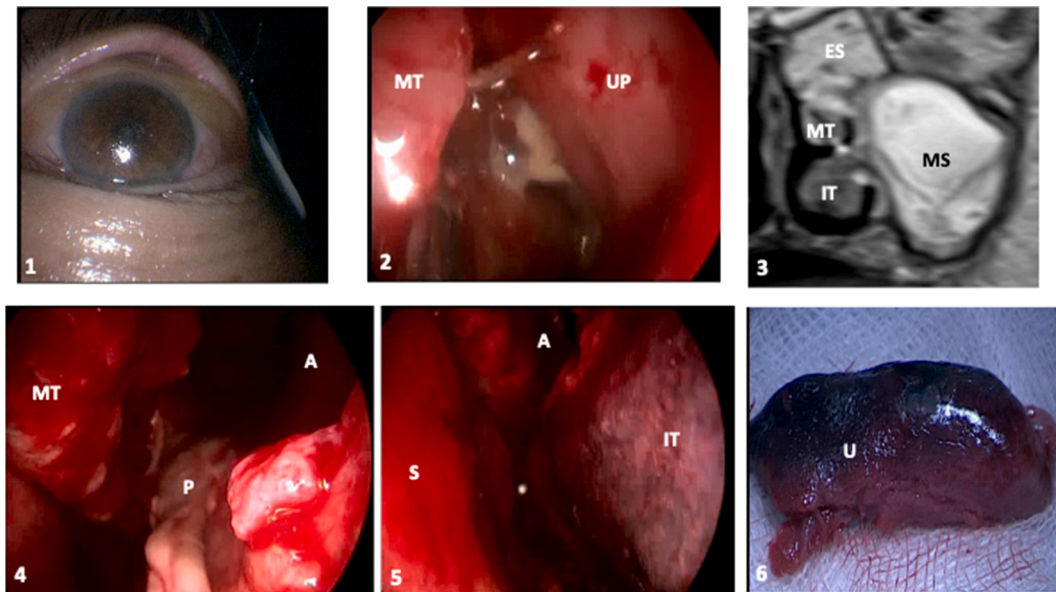


Fig. 2. Intra- and peri-operative images. 1 Left orbit with chemosis. 2 intraoperative image demonstrating pus discharging from middle meatus. 3 preoperative MRI identifying left maxillary and ethmoid sinus opacification. 4 intraoperative image with extraction of thick fibrous tenacious maxillary sinus collection being extracted from left maxillary sinus following antrostomy. 5 mottled appearance of left inferior turbinate. 6 excised inferior turbinate with surface ulceration. MT = middle turbinate. UP = uncinate process. ES = ethmoid sinus. IT = inferior turbinate. P = pus, thick and tenacious. A = antrostomy. S = septum. U = ulceration.

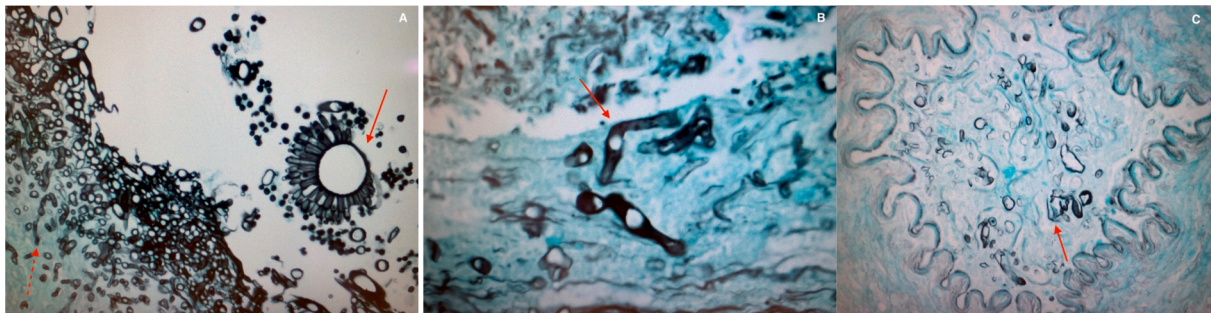


Fig. 3. Histology from surgical specimens. (A) fruiting bodies (solid arrow) and septate hyphae (dashed arrow) of *Aspergillus* [Grocott stain, 20x magnification]; (B) broad, aseptate hyphae of *Mucor* branching at 90 degrees (solid arrow) [Grocott stain, 20x magnification]; (C) hyphae of *Mucor* (solid arrow) within a blood vessel [Grocott stain, 40x magnification].

To clear diseased tissue, he required aggressive open surgery to debride the soft and bony tissues of the left hemi-face. He was therefore transferred to a specialist skull base surgical centre on day 31 where he underwent an extended maxillectomy and skull base clearance on day 37. Intraoperative findings were of a necrosed left maxilla, pterygoid muscles and periorbita, as well as necrotic dead bone when drilling the bony floor of the left middle cranial fossa. The foramen rotundum was full of necrotic tissue. Unfortunately, the patient deteriorated from a COVID pneumonitis perspective and required invasive ventilation in intensive care, where he passed away from COVID pneumonitis on day 47 of his illness.

Discussion

Mucormycosis is a rare and serious fungal infection caused by moulds of the order Mucorales, with *Rhizopus*, *Mucor* and *Rhizomucor* the most commonly implicated genera in human infections. Whilst found throughout the environment, it particularly causes disease in those who are immunocompromised or with diabetes mellitus (Kauffman and

Malani, 2007). One of the most devastating manifestations is severe rhino-orbital-cerebral infection, as demonstrated in our case, and overall mortality ranges from 25 to 62 percent despite antimicrobials or surgical intervention (Roden et al., 2005). It is therefore vital to have a high index of suspicion in those with suggestive signs or symptoms and initiate appropriate management promptly, including controlling risk factors such as hyperglycaemia and immunosuppression, along with use of antifungals such as amphotericin B, posaconazole or isavuconazole.

Due to how rapidly mucormycosis can destroy tissue, urgent referral for aggressive surgical debridement is a crucial step. As demonstrated by our case, serial imaging with CT and diffusion-weighted MRI is vital to characterise soft tissue and bony spread in mucormycosis (Sreshta et al., 2021), which in turn can aid prognostication and early referral to specialist centres.

There is currently renewed interest in mucormycosis due to its association with COVID-19. An autopsy series of ten patients who died from COVID-19 found one case of disseminated mucormycosis (Hanley et al., 2020), and there have been descriptions of the link between COVID-19 infection and other fungal infections such as invasive

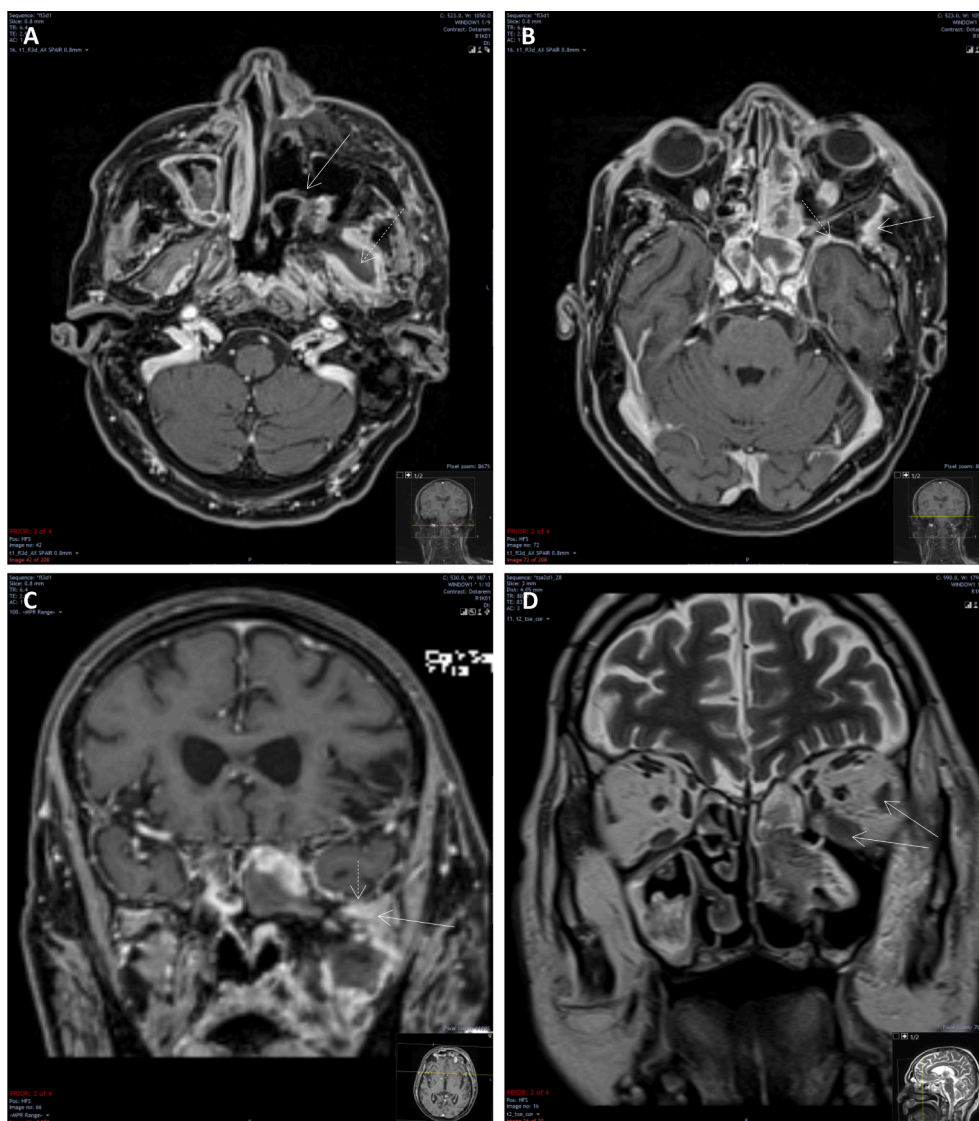


Fig. 4. Post-surgical MRI. (A) Axial post contrast T1 fat saturated sequence demonstrating left inferior turbinectomy and antrostomy (solid arrow) and worsening left masticator space enhancement with non-enhancing/necrotic left lateral pterygoid muscle (dashed arrow). (B) Axial post contrast T1 fat saturated and (C) coronal post contrast T1 fat saturated sequences, both demonstrating pathological enhancement extending superiorly into the temporal fossa and along the skull base (solid arrows) with asymmetric left middle cranial fossa dural enhancement (dashed arrow), suggesting intracranial extension. (D) Coronal T2 sequence demonstrating worsening asymmetric left inferior and lateral rectus oedema (solid arrows).

aspergillosis (Bartoletti et al., 2020). In particular, there has been an explosion of cases in India in the current COVID-19 wave, with catastrophic consequences on the local health system infrastructure (Stone et al., 2021).

The relationship between COVID-19 and mucormycosis is at present poorly understood (Chandra and Rawal, 2021; John et al., 2021). In an Indian case series of 187 patients, COVID-19-related hypoxaemia and improper glucocorticoid use were independently associated with mucormycosis (Patel et al., 2021). In India, there is widespread use of steroids for even mild cases, which may potentiate both an immunosuppressed state and poor diabetic control. COVID-19 itself may exacerbate hyperglycaemic states, with the link between COVID-19 and diabetic ketoacidosis being well described previously (Palermo et al., 2020). Furthermore, given that hospitals in India have been overwhelmed in this last wave of COVID-19, healthcare-associated mucormycosis remains a possibility, such as potentially contaminated ventilation systems (Walther et al., 2020). In addition, there may be possible risks associated with particular variants – in particular, the Delta COVID-19 variant (B.1.617.1), currently the predominant strain in both India and the UK (Torjesen, 2021).

Conclusion

We present a case of COVID-19 infection and associated mucormycosis. Our case demonstrates the devastating consequences of this condition, along with the complicating effects of concomitant COVID-19 infection. As the UK enters a new phase of the COVID-19 pandemic, it is crucial for UK clinicians to remain vigilant of the possibility of the link between COVID-19 and mucormycosis to ensure life-saving treatment can be rapidly instituted for this incredibly aggressive disease.

CRediT authorship contribution statement

Melissa Chowdhury: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Junko Takata:** Formal analysis, Writing – original draft, Writing – review & editing. **Issa Beegun:** Resources, Writing – review & editing. **Chris Burd:** Resources, Writing – review & editing. **Taranjit Tatla:** Supervision, Writing – review & editing. **Tumena Corrah:** Supervision, Writing – review & editing.

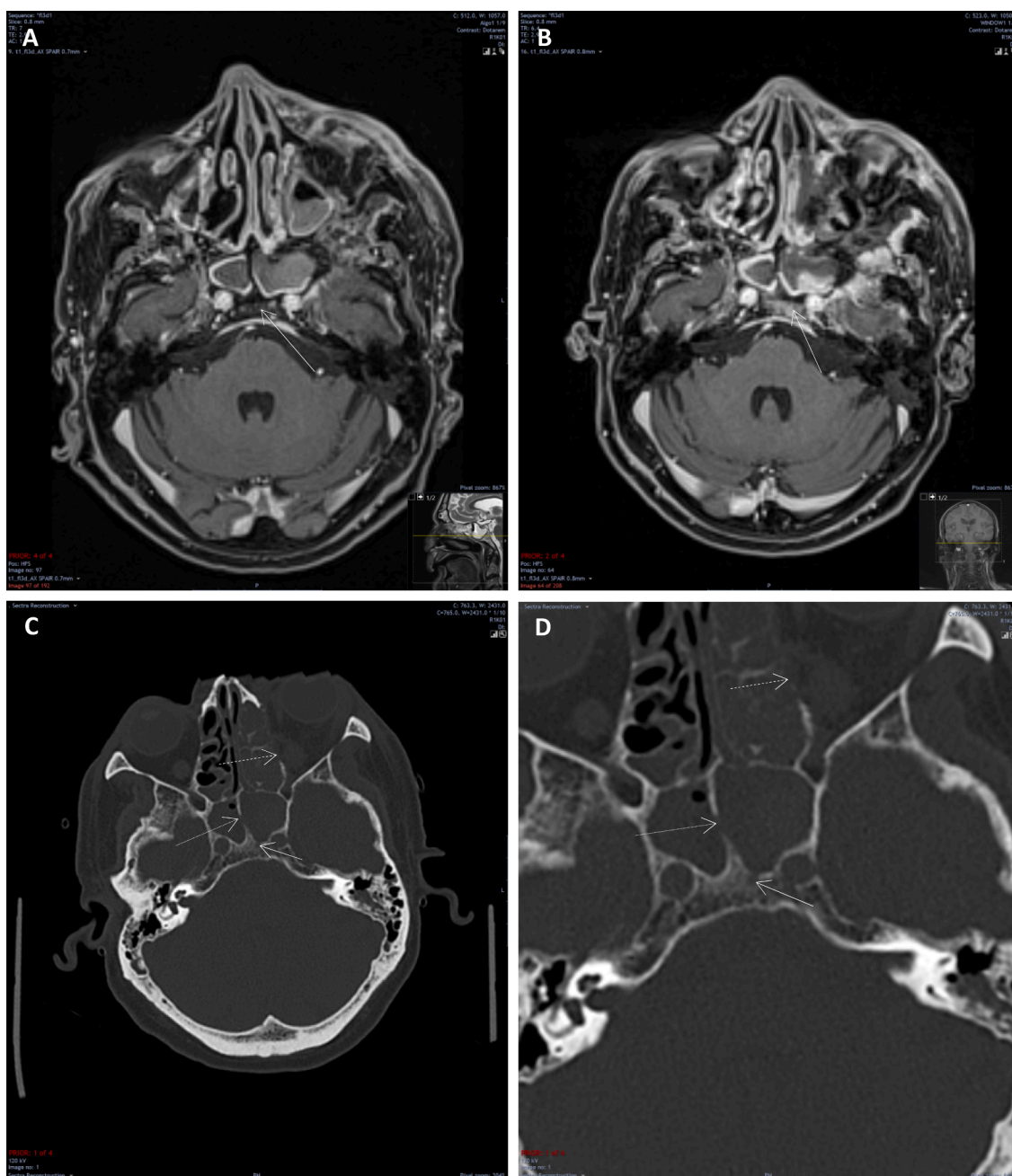


Fig. 5. Post-surgical CT and MRI. (A) Initial and (B) post surgery axial post contrast T1 fat saturated MRIs demonstrating normal clival marrow signal (A, solid arrow) and interval pathological clival marrow enhancement (B, solid arrow) suggesting skull base involvement. (C) Post surgery axial and (D) zoomed in axial CT images demonstrating subtle posterior left sphenoid locule wall erosive cortical defect (solid arrows), inter-sphenoid septal erosion (dotted arrows) and lamina papyracea erosion with asymmetric soft tissue (dashed arrows).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Consent for publication

Verbal and written consent gained from subject of case report.

References

- Bartoletti, M., Pascale, R., Cricca, M., Rinaldi, M., Maccaro, A., Bussini, L., et al., 2020. Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated

- patients: a prospective study. *Clin Infect Dis*. <https://pubmed.ncbi.nlm.nih.gov/32719848/>.
- Chandra, S., Rawal, R., 2021. The surge in Covid related mucormycosis. *J. Infect*. <https://pubmed.ncbi.nlm.nih.gov/34126158/>.
- Hanley, B., Naresh, K.N., Roufousse, C., Nicholson, A.G., Weir, J., Cooke, G.S., Thursz, M., Manousou, P., Corbett, R., Goldin, R., Al-Sarraj, S., Abdolrasouli, A., Swann, O.C., Baillon, L., Penn, R., Barclay, W.S., Viola, P., Osborn, M., 2020. Histopathological findings and viral tropism in UK patients with severe fatal COVID-19: a post-mortem study. *Lancet Microbe* 1 (6), e245–e253.
- John, T.M., Jacob, C.N., Kontoyiannis, D.P., 2021. When Uncontrolled Diabetes Mellitus and Severe COVID-19 Converge: The Perfect Storm for Mucormycosis. *J. Fungi*. (Basel, Switzerland). <https://pubmed.ncbi.nlm.nih.gov/33920755/>.
- Kauffman, C.A., Malani, A.N., 2007. Zygomycosis: An emerging fungal infection with new options for management. *Curr. Infect. Dis. Rep.* 9 (6), 435–440.
- Palermo, N.E., Sadhu, A.R., McDonnell, M.E., 2020. Diabetic Ketoacidosis in COVID-19: Unique Concerns and Considerations. *J. Clin. Endocrinol. Metab.* 105 (8), 2819–2829. <https://academic.oup.com/jcem/article/105/8/2819/5857202>.
- Patel, A., Agarwal, R., Rudramurthy, S.M., Shevkani, M., Xess, I., Sharma, R., et al., 2021. Early Release - Multicenter Epidemiologic Study of Coronavirus Disease-Associated Mucormycosis, India - Volume 27, Number 9—September 2021 - Emerging Infectious Diseases journal - CDC. *Emerg. Infect. Dis.* https://wwwnc.cdc.gov/eid/article/27/9/21-0934_article.
- Roden, M.M., Zaoutis, T.E., Buchanan, W.L., Knudsen, T.A., Sarkisova, T.A., Schaufele, R. L., Sein, M., Sein, T., Chiou, C.C., Chu, J.H., Kontoyiannis, D.P., Walsh, T.J., 2005. Epidemiology and Outcome of Zygomycosis: A Review of 929 Reported Cases. *Clin. Infect. Dis.* 41 (5), 634–653.
- Sreshtha, K., Dave, TarjaniVivek, Varma, DanduRavi, Nair, AkshayGopinathan, Bothra, N., Naik, MilindN, Sistla, SrinivasKishore, 2021. Magnetic resonance imaging in rhino-orbital-cerebral mucormycosis. *Ind. J. Ophthalmol.* [Internet]. 69 (7), 1915. https://doi.org/10.4103/ijo.IJO_1439_21.
- Stone, N., Gupta, N., Schwartz, I., 2021. Mucormycosis: time to address this deadly fungal infection. *Lancet Microbe*. <http://www.thelancet.com/article/S2666524721001488/fulltext>.
- Torjesen, I., 2021. Covid-19: Delta variant is now UK's most dominant strain and spreading through schools. *BMJ* 373, n1445. <https://www.bmj.com/content/373/bmj.n1445>.
- Walther, G., Wagner, L., Kurzai, O., 2020 Oct 1. Outbreaks of Mucorales and the Species Involved. *Mycopathologia*. 185 (5), 765–781.