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Case Report

Non-surgical management of chronic granulomatous invasive fungal sinusitis with intracranial extension a case report and literature review

Nicholas G. Candy[1]*, Anushia Ashokan[2], Wan Yin Lim[3], Sarah E. Kidd[4], Craig James[5], Amal Abou-Hamden[1], Alkis J. Psaltis[6]

[1]Department of Neurosurgery, Royal Adelaide Hospital, South Australia, Australia
[2]Department of Infectious Diseases, Royal Adelaide Hospital, South Australia, Australia
[3]South Australian Medical Imaging, Royal Adelaide Hospital, South Australia, Australia
[4]National Mycology Reference Centre, Microbiology and Infectious Diseases, SA Pathology, South Australia, Australia
[5]Department of Anatomical Pathology, Clinpath Pathology, South Australia, Australia
[6]Department of Otolaryngology and Head and Neck Surgery, Royal Adelaide Hospital, South Australia, Australia

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***Correspondence:**
Dr. Nicholas G. Candy,
E-mail: nicholas.g.candy@gmail.com

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ABSTRACT

Chronic granulomatous invasive fungal sinusitis (CGIFS) is a rare manifestation of the heterogeneous disease process of fungal rhinosinusitis that is traditionally managed with some form of resective or debulking surgery. Historically, these were invasive transfacial resections. With the development of endoscopic surgery this treatment has become less invasive, but surgery still forms a major component of management. It is a rare disease that usually only occurs in dry subtropical areas. We describe the case of a female in her 30's who presented with progressive headache and facial paresthesia. Workup demonstrated a large destructive lesion centred on the left sphenoid sinus invading the orbit and middle cranial fossa. The patient underwent urgent biopsies with a presumed diagnosis of an invasive malignancy. Upon identifying fungal organisms on culture the patient was commenced on anti-fungal treatment. We describe the first medically managed case of CGIFS with orbital and intracranial extension and perform a review of the contemporary literature to better understand this rare and challenging condition.

Keywords: Endoscopic surgery, Fungal sinusitis, Chronic sinusitis, Skull base surgery

INTRODUCTION

Chronic granulomatous invasive fungal sinusitis (CGIFS) is a rare manifestation of the heterogeneous disease process of fungal rhinosinusitis. CGIFS is a rare disease with most cases being reported in dry subtropical areas such as: Sudan, India, Saudi Arabia and Pakistan.[1]

Initially classified by DeShazo et al in 1997 based on histopathological appearances. *Aspergillus flavus* was identified as the most common causative species in cases of CGIFS.[2] In 1996 Rhaman et al defined a classification system and proposed a tiered surgical management algorithim.[3]

This approached involved increasingly invasive transfacial approaches as well as consideration of a craniotomy depending on the stage of disease. This approach was updated by Rupa et al in 2014.[4] They modified the staging to involve endscopic or open resection for lower stage disease, but combined modality resection in high stage disease. We described the first medically managed case of CGIFS with orbital and intracranial extension.

CASE REPORT

This case has been reported in line with CARE guidelines.[5] A 34-year-old female initially presented to her local GP describing headaches and left sided facial paresthesia involving the left hard palate and mouth. This had been progressive over at least 1 month. She had no medical background other than a previous COVID-19 infection 1 to 2 months earlier, for which she did not require any treatment. She emigrated from Pakistan in the 1980's and was last visiting between December 2021 and March 2022. She had not taken any steroids or other immunosuppressive medication and had no family history of autoimmune disease. On examination at presentation, she had diplopia on right lateral gaze and reduced light sensation over left V1 and V2. Otherwise, the remainder of her exam was normal. She underwent neuroimaging imaging which demonstrated a destructive process centred in the left sphenoid sinus with extensive intracranial extension (Figure 1). On MRI the lesion was predominantly T2 hypointense and mildly T1 hyperintense to brain parenchyma, with no significant diffusion restriction. Avid, homogeneous enhancement following administration of contrast. The lesion involved both cavernous sinuses and middle cranial fossae, with greater extent on the left side associated with temporal lobe vasogenic oedema. CT showed hyperdense opacification of the sphenoid sinuses with surrounding sclerosis, indicative of chronic sinus inflammation. Differentials initially raised included primary sinonasal undifferentiated carcinoma (SNUC) or secondary tumour such as plasmacytoma or melanoma. In the absence of significant diffusion restriction, nasopharyngeal carcinoma and lymphoma felt less likely. She was urgently referred to a skull base otolaryngologist and subsequently underwent an urgent endoscopic endonasal biopsy under general anaesthesia. At the time of surgery, the macroscopic appearance of the mass was suspicious for a neoplastic pathology, given the fibrotic nature of the mass and the lack of any purulence (Figure 2).

The biopsy results demonstrated extensive fibrosis with non-caseating and non-suppurative granulomas. The granulomas comprised epithelioid histiocytes, frequent multinucleate giant cells of foreign body type plus admixed lymphocytes, whilst there were also tissue plasma cells, occasional eosinophils and a few neutrophils without abscess formation. There were abundant tissue fungal organisms, free lying within fibrotic foci and within the cytoplasm of giant cells. The fungal elements, seen with both Periodic Acid-Schiff/diastase (PAS) and Grocott methenamine silver (GMS) stains, appeared quite broad and infrequently branching although there were some true septations. This was not consistent with the traditional appearances of Aspergillus species or Mucorales. Endospores were not seen, nor was there angioinvasion, perineural spread, extensive tissue necrosis or coexistent neoplastic pathology (Figure 3). Based on these findings a presumptive diagnosis of chronic granulomatous invasive fungal disease was made with additional tissue samples sent for bacterial and fungal culture including *Aspergillus* PCR, which was positive and cultured *Aspergillus flavus* complex. She was transferred to a tertiary hospital for multi-disciplinary team management. During this admission the patient underwent extensive workup for an underlying immunosuppressive condition, which was unremarkable. She was initially commenced on empiric ceftriaxone, vancomycin and liposomal amphotericin B. Her antibiotics ceased once fungal cultures returned positive for *Aspergillus flavus*. She did not tolerate IV liposomal amphotericin B and was switched to oral voriconazole once fungal susceptibilities were known and voriconazole levels reached a therapeutic level. A trough level of 2-4 mg/l was targeted. Antifungal susceptibilities determined using the sensititre yeast one broth microdilution test demonstrated MICs to amphotericin B, voriconazole, and posaconazole of 4 µg/ml, 0.25 µg/ml, and 0.12 µg/ml, respectively.

Within a few days of commencing voriconazole, the patient's neurological and cavernous sinus symptoms completely resolved and her only remaining symptom was headache. Her case was discussed at a skull base multi-disciplinary meeting, with the consensus favouring non-surgical management and continuation of her IV antifungal therapy given her dramatic clinical improvement. Shortly after being discharged from hospital, the patient developed hepatotoxicity which was thought to be secondary to voriconazole. Her therapy was switched to posaconazole CR and she remains on this with no issues. MRI follow-up at 5 months post-treatment demonstrated significant improvement in burden of disease, with a near-complete resolution of the intradural and cavernous sinus disease and significant improvement in the degree of disease in the paranasal sinuses (Figure 4). She is planned for a minimum of 6-9 months of treatment until the resolution of disease on imaging.

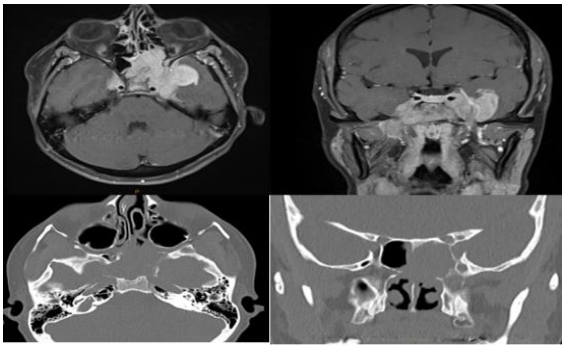

Figure 1: Top images demonstrate T1 post Gad axial and coronal MRI through the level of the sphenoid sinus and middle cranial fossa. The contrast enhancing lesion can be seen invading the cavernous sinuses bilaterally, the middle cranial fossa on the left with associated vasogenic oedema as well as filling the spenoid sinus. Bottom images demonstrate a bone window CT with axial and coronal slices through the same areas as above showing local bony destruction concerning for an invasive process.

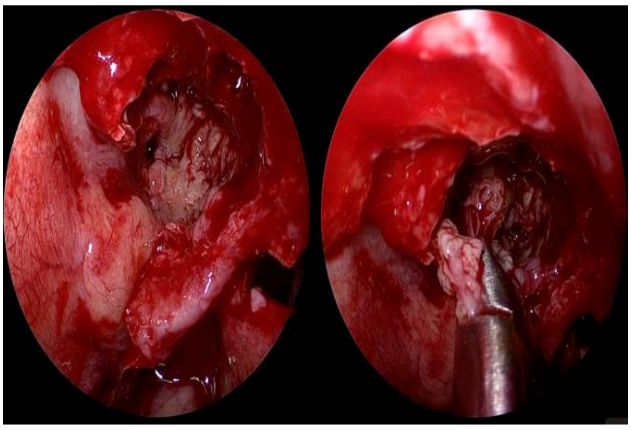

Figure 2: Intra-operative endoscopic picture demonstrating the fibrous mass extending through the sphenoid sinus into the posterior ethmoid cavity, with another picture demonstrating a biopsy of the fibrous mass.

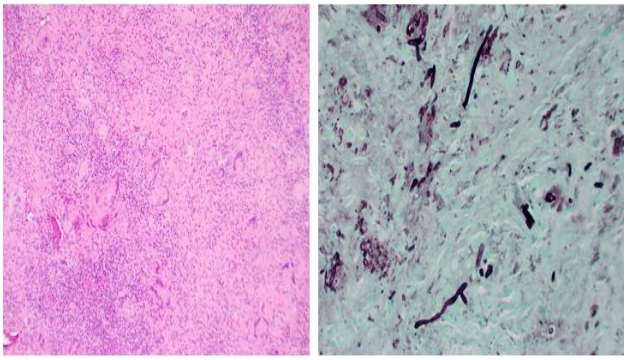

Figure 3: Left image demonstrates H and E (at 100X) showing sinus fibrosing granulomatous inflammation with no associated suppuration or necrosis. Right image demonstrates a GMS stain (at 200X) showing baggy but focally branching septate fungal hyphae within stroma. Culture and PCR subsequently confirmed *Aspergillus flavus*.

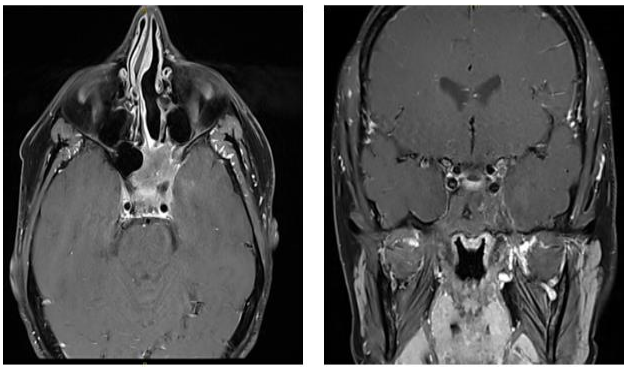

Figure 4: T1 post Gad axial and coronal MRI through the sphenoid sinus. Demonstrating appearance of disease burden 5 months after treatment. There is near complete resolution of the intra-canial disease with significant reduction of the paranasal sinus disease.

DISCUSSION

CGIFS is a rare disease with only a small number of reported cases outside of dry subtropical areas.

Rhaman et al in 1996 defined a staging scheme based on their experience from 9 cases at a hospital in Saudi Arabia.[3] This series defined 3 progressive stages: Stage I sinonasal, stage II cranial and finally stage III intracranial. Stage I disease underwent radical resection by either a lateral rhinotomy or external ethmoidectomy. Stage II disease was managed by a tailored craniofacial resection. Finally, stage III disease was managed with combined open craniofacial resection and craniotomy to resect intracranial collections.

The approach to management of CGIFS was updated in 2014 when Rupa et al[4] published their experience in the management of patients presenting to an Indian hospital. They reported on 14 patients managed between 2006 and 2014. They presented a modified staging scheme to what Rhaman et al originally devised.[3] Surgery formed a major part of their management approach, with stage 1 disease receiving endoscopic resection and stage 2 disease undergoing either endoscopic or open resection for partial or total maxillectomy. Stage 3 disease was managed with combined endoscopic and open craniofacial resection. Antifungal treatment commonly involved amphotericin and itraconazole. Voriconazole was prescribed to 4 patients, and an additional 2 patients who failed amphotericin treatment.

In 2023 Rupa et al published a comprehensive review of management approaches, highlighting the significant variation in the literature.[1] Radical open resection formed the mainstay of management prior to the advent of the endoscope and modern anti-fungal treatments. Currently, the most common approach appears to involve the removal of grossly involved tissue without violating any natural planes such as dura or periorbita. Interestingly, contemporary case series have not demonstrated any difference in outcome between different stages of disease. In fact, our case is the only example where biopsy alone with medical management and close clinical and radiological follow-up represents an effective treatment alternative.

The association between acute invasive fungal sinusitis and patients with antecedent COVID-19 infection has been reported in the literature.[6,7] This association is thought to relate to a decrease in CD4 and CD8 T cells. These patients typically have associated comorbidities such as diabetes mellitus, haematological malignancy or steroid use. There is only 1 reported case in the literature of CGIFS post-COVID-19 and they had a background of diabetes mellitus.[8] Compared to that report, our patient presented after a similar period of time following COVID-19 infection. Given this is only the second reported case of CGIFS following COVID-19, it is uncertain if there is a relationship between these two infections.

There is no data demonstrating the efficacy of different anti-fungal treatments in the management of CGIFS due to the rarity of the pathology. Evidence to guide management comes from 2 trials that examined different anti-fungal medications in the treatment of invasive aspergillosis in immunosuppressed patients. Herbrecht et al in 2002 published a randomised controlled trial comparing outcomes in patients suffering invasive aspergillosis secondary to immunosuppression managed with either amphotericin B or voriconazole.[9] They demonstrated that initial treatment with voriconazole led to better response and improved survival compared to amphotericin. Recently Maertens et al examined the outcomes of voriconazole compared to posaconazole in a similar cohort of patients.[10] They demonstrated similar outcomes, but an improved side effect profile in patients receiving posaconazole. Voriconazole is usually the recommended first-line agent of choice for invasive aspergillosis. Posaconazole is an appropriate second-line agent if hepatotoxicity to voriconazole develops.

The other reported case of CGIFS post-COVID-19 was managed initially with endoscopic bilateral maxillary antrostomy, frontal sinus trephination and debridement of frontal and maxillary mucosa.[8] Our case is different given that debulking surgery was not undertaken due to the patient's initial significant improvement in medical management alone. Had this not been the case, salvage surgery would have been recommended. Our case demonstrates the potential to manage these cases with biopsy and antifungal treatment alone, an approach that is different to the current body of literature.[1]

CONCLUSION

We present the first case of chronic granulomatous invasive fungal sinusitis in Australia, and the second case related with a COVID-19 infection. Our case also suggests there is a potential to manage cases with significant intracranial invasion with anti-fungal treatment alone, potentially avoiding the morbidity of extensive surgical resection.

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