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Chronic granulomatous invasive fungal maxillary sinusitis: Report of the first case from South Africa

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CASE REPORT

A 37-year-old South African woman was referred to an ear, nose and throat (ENT) specialist with a history of painful maxillary sinusitis with nasal obstruction. Five days prior to her presentation, she was admitted to a hospital emergency unit with clinical symptoms of headache, nausea, rigor, red eyes, body pain (back and chest pain) and photophobia. She was subsequently diagnosed with a viral infection, and was investigated to exclude the possibility of meningitis. Her blood test results revealed a shifting raised neutrophil count (9.6) and creatinine (79) but a CRP of less than 5, and further test results were normal. A computed tomography (CT) scan showed no evidence of focal brain lesions, cerebral oedema or hydrocephalus. However, there were radiological features of an enlarged left maxillary sinus ostium, which the radiologist reported as suggestive of previous sino-nasal surgery. There was also mucosal thickening of the maxillary sinuses. The mucosal lining was significantly thicker on the left side, where high density material was present. It was believed that the latter might indicate fungal sinusitis. The patient reported that she had no prior sinus surgery but had had two episodes of "sinusitis" with nasal obstruction and sneezing, that would leave a bad smell in her throat for two weeks. She also mentioned that the use of over-the-counter medication Sinutab had alleviated the sinusitis symptoms. At the time of her presentation, there was no nasal obstruction and no pain related to the sinuses. On examination anterior rhinoscopy and flexible fibre-optic endoscopy was completely normal bilaterally, with no signs of sinusitis and, in particular, no discharge from the left maxillary antrum. There was mild deviation of the nasal septum to the right. Review of the CT scan confirmed the expanded left maxillary sinus ostium and opacification of the enlarged left maxillary antrum, involving the lower two thirds of the sinus. It appeared that there were some "double densities" within the opacification with bulging of its superior margin, in keeping with a cystic lesion (Figure 1). The patient was therefore booked for endoscopic removal of the tissue in the left maxillary antrum. A standard left middle meatus antrostomy was done using the endoscopic approach, which showed a polyp with debris in the maxillary antrum. The debris was of the nature of caseous material. The polyp and the caseous material were removed, placed in a formalin container and submitted to the pathology laboratory for histological evaluation.

Microscopic examination of the tissue from the maxillary sinus revealed fragments of sinonasal mucosa with granulomatous inflammation (Figure 2a). The granulomas consisted of Langhans-type giant cells with central areas of necrosis (Figure 2b). The giant cells contained broad and acutely branching septated fungal hyphae with fruiting bodies, consistent with Aspergillus (Figure 2c). Periodic Acid Schiff (PAS) and Grocott Methanamine Silver (GMS) stains were done to best highlight the fungal organisms (Figures 2d-2f). Based on the clinical, radiologic and microscopic features, a diagnosis of chronic granulomatous invasive fungal sinusitis (CGIFS) was established.

On follow-up one week after the surgery the patient was well, and had no pain or discomfort in relation to the maxillary antra. In light of the absence of significant symptoms it was considered unnecessary to admit her for intravenous antifungal therapy, and treatment was initiated with oral voriconazole: a loading dose of 400mg twice a day for three days, followed by 200mg twice a day for one month, with follow-up at that time.

DISCUSSION

Fungal sinusitis is classified into two main groups – non-invasive and invasive. Each of these groups has three subgroups – see Table 1.

Table 1. Classification of fungal sinusitis

Non-invasive fungal sinusitis	Invasive fungal sinusitis
Allergic fungal sinusitis	Acute invasive fungal sinusitis
Fungal ball	Chronic invasive fungal sinusitis
Saprophytic fungal sinusitis	Chronic granulomatous fungal Sinusitis

Invasive fungal sinusitis can be acute or chronic.[1] Acute invasive fungal sinusitis (AIFS) is an aggressive rapidly invasive fungal sinusitis, often caused by hyphae form of the fungi *Zygomycetes* (such as *Rhizopus* and *Mucor*). AIFS has high mortality rates (50-80%) and is often seen in immunocompromised patients (commonly diabetics, HIV-positive patients and those with haematological malignancies).[2,3] The chronic form is further subdivided into non-granulomatous and granulomatous subtypes.[1] Chronic granulomatous invasive fungal sinusitis (CGIFS) is extremely rare and has a protracted clinical course, with progressive

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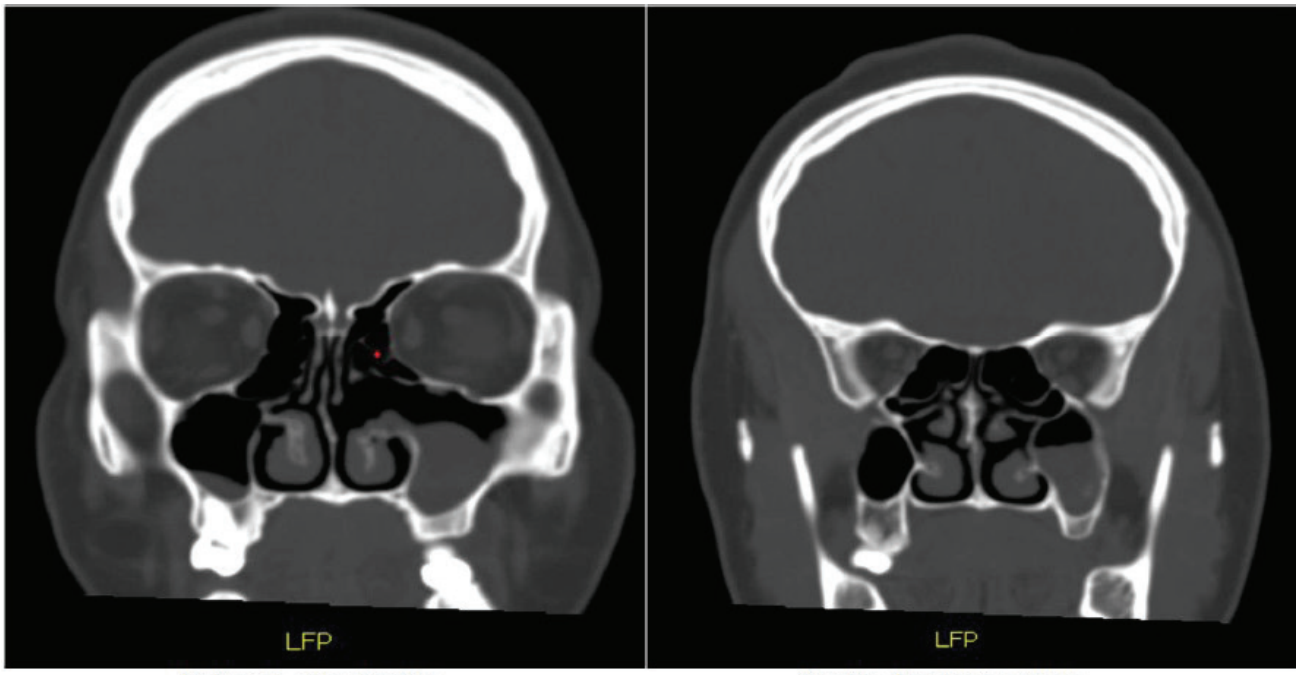

Enlarged antrostomy L | Double density L antrum

Figure 1. CT scan shows an expanded left maxillary sinus ostium and the presence of double densities in the left enlarged maxillary sinus.

invasion and destruction of the paranasal sinuses and the adjacent structures.[4-7] CGIFS primarily affects young to middle-aged immunocompetent adults with a slight female predominance.[8] The majority of CGIFS cases are diagnosed in patients from subtropical regions of India, Sudan, Pakistan and Saudi Arabia.[4-7] CGIFS is very rare in the western world with isolated cases reported from the US and the Balkan region.[4-7,9] To the best of our knowledge this is the first case report from the Western Cape region of South Africa. Aspergillus flavus is the main aetiologic agent; however, Aspergillus nidulans has been isolated from a few cases of CGIFS.[8] CGIFS predominantly occurs in maxillary and ethmoid sinuses, with the ethmoid sinus being the most common site of involvement.[10] In general, patients with CGIFS present with symptoms of chronic sinusitis (CS), namely nasal congestion, mucus discharge, postnasal drip, reduced sense of smell, facial pain/pressure and toothache.[9] In a study from Saudi Arabia, nasal obstruction was the most common presenting symptom in 87% of the cases.[10] Therefore, CGIFS is often misdiagnosed as CS, with consequent delay in treatment with significant morbidity. Although radiological imaging may suggest the possibility of CGIFS, with the characteristic feature being the so-called "double densities" (opacification of the sinusitis with denser and less dense areas), definitive confirmation of CGIFS requires histopathological evaluation and microbiological studies (eg culture).[1] Histological assessment of representative samples from CGIFS patients reveals granulomas with Langhans-type giant cells, surrounded by a rim of chronic inflammatory cells.[1] The giant cells contain broad and acutely branching septated Aspergillus hyphae with fruiting bodies.[1] The fungal hyphae are best highlighted on PAS and GMS special histological stains. The histological differential diagnosis of CGIFS includes other granulomatous inflammatory diseases of the sino-nasal region such as tuberculosis, leprosy, treponematosis, histoplasmosis, cryptococcosis, sarcoidosis and, finally, NK/T-cell lymphoma, which may have a vague granulomatous appearance.[11] Ziehl-Neelsen (ZN) and Fite special histological stains help to exclude mycobacterial infections, while Treponema immunohistochemistry (IHC), microbiological culture, chest imaging for hilar adenopathy and CD56 and EBERISH IHC help exclude treponematosis, histoplasmosis, cryptococcosis, sarcoidosis and NK/T-cell lymphoma respectively.[11] Due to the rarity of CGIFS, there is no standard treatment protocol. However, the Infectious Diseases Society of America recommends voriconazole as the drug of choice for the treatment of invasive Aspergillosis.[12] Indeed, some studies have found oral voriconazole, 200mg twice daily, with a mean duration of therapy of five to six months, effective in eradicating the disease.[8] Supplemental surgical debridement may help reduce the fungal load, allowing for shorter recovery time.[8] Death due to GCIFS is very rare and is usually seen in immunocompromised patients with sphenoid sinus involvement with intracranial extension.[8]

CONCLUSION

This is the first case report of CGIFS from the Western Cape region of South Africa. CGIFS represents an important diagnostic dilemma for the unwary ENT and oral health care professional due to its rarity and overlapping symptomatology to CS (eg nasal obstruction, toothache etc), with associated significant morbidity. A multidisciplinary approach is recommended for all non-resolving cases of CS, comprising haematological tests, radiological imaging, flexible endoscopy, histological examination and microbiological culture.

COMPLIANCE WITH ETHICAL STANDARDS

Funding

This is a case report and no funding was required.

Conflict of interest

All authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with

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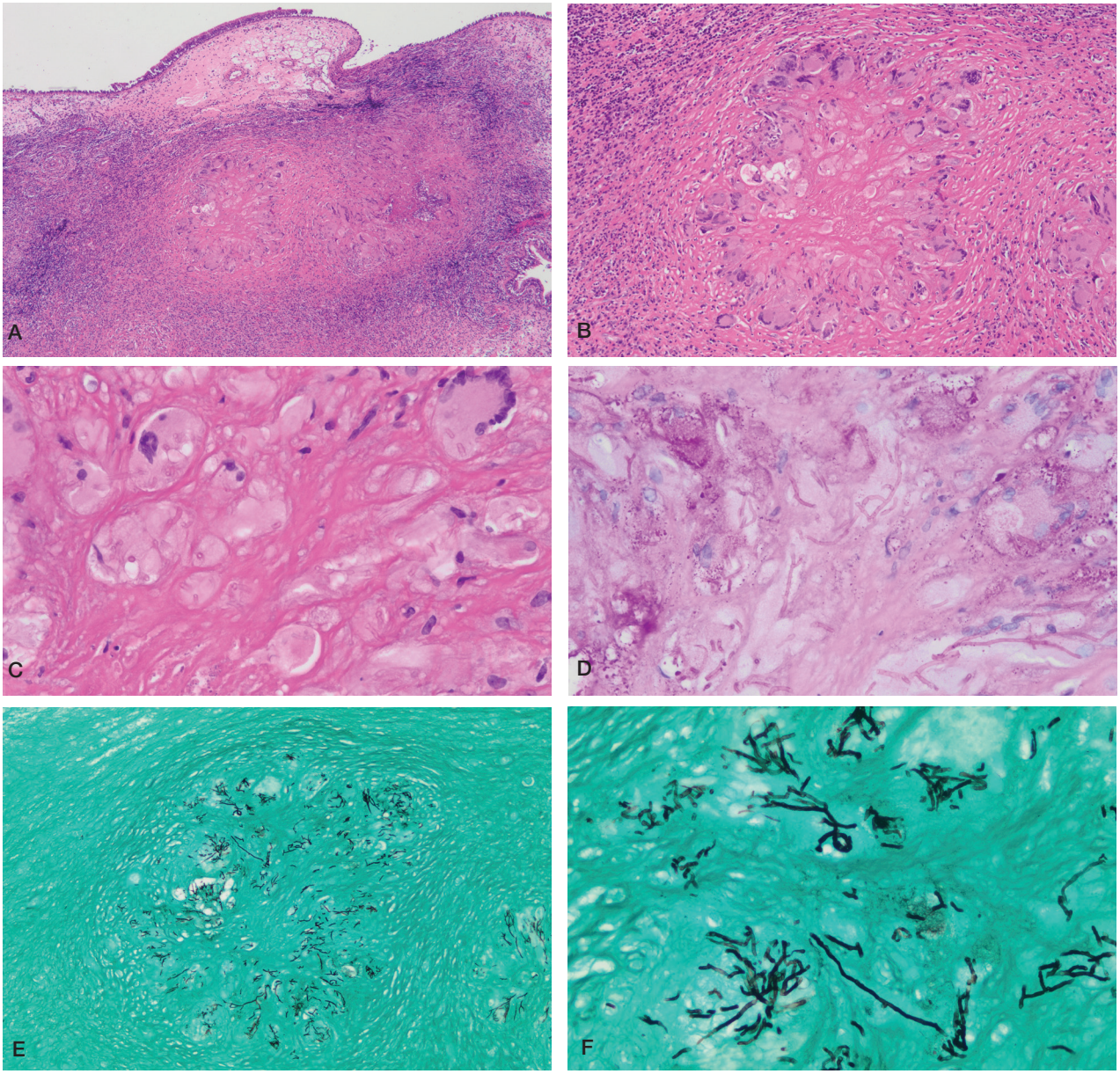

Figure 2(a). The photomicrograph shows a fragment of sinus mucosa surfaced by respiratory-type epithelium. The subepithelial connective tissue exhibits several necrotising granulomas (H&E, x10). **(b)** The image shows a granuloma consisting of multinucleated Langhans-type giant cells with a central area of necrosis (H&E, x20). **(c)** The giant cells contain hyphae with fruiting bodies (H&E, x40). **(d)** Acutely branching Aspergillus hyphae with fruiting bodies (PAS, x40). **(e,f)** The Grocott Methanamine Silver stain highlights the outline of a granuloma with black staining acutely branching Aspergillus hyphae with fruiting bodies (GMS, x40).

the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

There are no patient identifiers in this case report and informed consent was obtained from the patient.

Consent for publication

For this type of study consent for publication is not required.

Availability of data and materials

All data sets and research materials are available for revision on request.

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