Original Research Article

Chronic granulomatous invasive fungal rhinosinusitis in Nigeria: challenges of management

Chinyere N. Asoegwu[1,4]*, Rita O. Oladele[2,4], Okezie O. Kanu[3,4], Clement C. Nwawolo[1,4]

[1]Division of Otorhinolaryngology, Department of Surgery, College of Medicine, University of Lagos, Lagos, Nigeria
[2]Department of Medical Microbiology and Parasitology, College of Medicine, University of Lagos, Lagos, Nigeria
[3]Division of Neurosurgery, Department of Surgery, College of Medicine, University of Lagos, Lagos, Nigeria
[4]Lagos University Teaching Hospital, Lagos, Nigeria

*Correspondence:
Dr. Chinyere N. Asoegwu,
E-mail: casoegwu@unilag.edu.ng

ABSTRACT

Background: Chronic granulomatous invasive fungal rhinosinusitis affects mainly immunocompetent patients and has been widely reported in tropical regions such as South East Asia and North Africa. Nigeria has a tropical climate, however, there is paucity of data on this disease condition in Nigeria. This study documents the clinical, diagnostic, therapeutic challenges of managing patients with this condition in Nigeria.

Methods: A retrospective study of patients diagnosed and treated for chronic granulomatous invasive fungal rhinosinusitis between 2010 and 2019. Diagnosis was based on clinical presentation, computed tomographic scan findings and confirmed by histopathology and/or microbiology results.

Results: Ten patients aged 12 to 49 years with mean age of 33.9±13.8 years were studied. Male to female ratio was 2.3:1. All were immunocompetent. Duration of symptoms before presentation ranged from 3 months to 8 years with a mean duration of 3.5±2.4 years. Commonest clinical presentation was unilateral proptosis 80% followed by nasal mass 50%. Commonest sinus involved was the ethmoid (80%). There was orbital extension in 70% and intracranial involvement in 50%. Aspergillus species was the commonest fungal agent cultured. Treatment was by surgical excision followed by antifungal drugs. Some of the challenges we encountered in the management included; late presentation, delay in diagnosis, limited experience in histopathologic and mycology diagnosis and high cost of treatment amidst scarce resource.

Conclusions: Chronic invasive granulomatous rhinosinusitis is not rare in Nigeria. A high index of suspicion is however needed for the diagnosis. Development of a National management protocol for this disease is recommended to avoid misdiagnosis.

Keywords: Granulomatous invasive fungal-rhinosinusitis, Nigeria, *Aspergillus*-species, Antifungal agents

INTRODUCTION

Invasive fungal rhinosinusitis (IFRS) is defined as rhinosinusitis caused by fungal infection with the invasion of the mucosa, submucosa and underlying structures by fungal hyphae. It is classified into acute invasive fungal rhinosinusitis (AIFRS) and chronic invasive fungal rhinosinusitis (CIFRS) based on the duration of the disease. CIFRS is divided into chronic granulomatous invasive fungal rhinosinusitis (CGIFRS) and chronic non-granulomatous invasive fungal rhinosinusitis (CNGIFRS).[1,2] CGIFRS is uncommon and is rarely reported among Caucasians. It affects mostly immunocompetent patients predominantly in countries with tropical climates such as South East Asia and North Africa and South-Western states of USA.[3-6] *Aspergillus flavus* is the most commonly isolated pathogen of CGIFRS in some tropical countries such as India,

Pakistan and Sudan and was also isolated in their open air.[6-10]

In the early stages of CGIFRS, clinical presentations and radiologic findings are not easily differentiated from other types of rhinosinusitis.[11] In advanced disease stage, their presentations mimic malignant tumors of the nose and paranasal sinuses. Computed tomography (CT) scan findings are those of mottled densities with irregular bone destruction involving one or more unilateral sinuses which is similar to findings in malignancies of the nose and paranasal sinuses.[6,11-13] Thus, a high index of suspicion is required for the diagnosis. Histologic evidence of non-caseating granuloma with invasion of branching fungal hyphae is the gold standard for the diagnosis of CGIFRS.[2] Microscopy, fungal culture, or Polymerase chain reaction methods are used to determine the specie of fungus. Serial surgical debridement and systemic amphotericin-B based antifungal therapy with voriconazole is the recommended treatment.[14]

Though CGIFRS has been increasingly reported in Southeast Asia and North Africa, there is a paucity of data from Sub-Saharan Africa and Nigeria in particular.[15] We present a descriptive analytical study of the clinical presentations, radiologic features, pathology and mycology, treatment modalities and the challenges encountered in the management of CGIFRS. This study is to help raise the awareness of the presence of CGIFRS in Nigeria and to guide Otolaryngologists in the diagnosis and management of this pathology in our communities in Nigeria and Sub-Saharan Africa.

METHODS

This study was carried out in Lagos University Teaching Hospital (LUTH) one of the two major tertiary care teaching hospitals in Lagos state. This hospital serves a large, urban population of approximately 21 million people of a mixed population of all tribes and social class in Nigeria. It is a 76-bed facility with all sub-specialties.

Study population

The medical record of all patients who were diagnosed of CGIFRS in the department of ENT, LUTH between January 2010 and December 2019 were reviewed for clinical presentation, radiologic findings, surgical procedures, histopathologic findings, fungal culture results, antifungal drugs and treatment outcome. Patients who had positive histopathology results for CGIFRS and or positive fungal culture results were included in the study. Duration of follow up was calculated from the date of commencement of treatment post histologic diagnosis.

Diagnostic criteria

Details extracted from the clinical notes included symptoms and signs at presentation, duration of disease before presentation, sinuses involved and extent of the disease from the CT scan radiologic investigation, specimen histopathology result of non-caseating granuloma with fungal hyphae surrounded by inflammatory cells, and positive fungal culture result and identification of fungal isolates.

Treatment modalities were by endoscopic and open surgery followed by antifungal therapy. Surgical debridement aimed to completely remove all infected tissue elements. The choice of surgical approach was determined by the extent of the disease based on radiologic information and the presence of facial deformities.

Statistical analysis

Descriptive statistics frequency and percentages were reported for categorical variables.

Written consent was obtained from those whose pictures were used. Approval for the study was obtained from the Lagos University Teaching Hospital Health Research Ethics Committee (LUTHHREC) with Reference ADM/DCST/HREC/APP/3193. Data was analyzed using Statistical Package for Social Sciences (SPSS) version 20 (IBM).

RESULTS

A total of 10 patients aged 12 to 49 years with mean age of 33.9±13.8 years were studied. Male to female ratio was 2.3:1. All participants were immunocompetent, dwelt in urban areas and were either civil servants or business men/women and students. One patient worked in a textile company, another sold textiles, one was a battery charger and dealt with acid, another was a farmer, two were students the remaining four were civil servants. The description of their home environment was not available. Duration of symptoms before presentation ranged from 3months to 8 years with a mean duration of 3.5±2.4 years. Though a 10 year study, the majority (80%) were diagnosed in the last 5 years.

Clinical presentation patterns

The clinical presentation patterns varied and were dependent on the sinuses involved and the extent of the disease. It included unilateral proptosis, nasal mass, cheek swelling, headache, orbital pain and facial pain with some having background chronic rhinosinusitis (Table 1).

Radiologic findings

All the sinuses were involved to a different extent. There was unilateral multi-sinus involvement of an average of two sinuses except for a case of frontal bossing involving frontal sinuses bilaterally (Table 2).

Table 1: Clinical presentation patterns.

Clinical presentation	N (%)
Background chronic rhinosinusitis with brownish or blackish rhinorrhea	5 (50.0)
Proptosis (unilateral)	8 (80.0)
Nasal mass	7 (70.0)
Cheek swelling	4 (40.0)
Frontal bossing	1 (10.0)
Headache/ facial/ orbital pain	6 (60.0)

Table 2: Computed tomographic scan findings.

Anatomic subsite involvement	N (%)
Nasal cavity	7 (70.0)
Maxillary sinus	5 (50.0)
Ethmoidal sinus	8 (80.0)
Frontal sinus	5 (50.0)
Sphenoidal sinus	3 (30.0)
Bilateral involvement (frontal sinus)	1 (10.0)
Bone destruction	10 (100.0)
Orbital extension	7 (70.0)
Intracranial involvement	5 (50.0)
Infratemporal/ pterygopalatine fossa involvement	1 (10.0)

Histopathology and mycology findings

All had their specimen sent for histopathology and mycology studies. All had histopathology results consistent with granulomatous formation but fungal hyphae were detected in only 8 (80.0%) specimens. Positive mycology result (fungal culture) was obtained in 4 (40%) cases. Only 2 patients had both positive histopathology and mycology results (Table 3).

Treatment and outcome

All the patients had surgical treatment followed by antifungal treatment. Seven (70%) of the 10 patients had transnasal endoscopic surgery with a good clearance of the disease. Open surgery was preferred in the other three (3) patients with visible deformities and included frontoethmoidectomy in one patient who had repeat surgery, lateral rhinotomy in one patient and partial maxillectomy with the clearance of Infratemporal/ pterygopalatine fossae. All the patients received either Itraconazole or Voriconazole or both at different times. Four (4) of the patients with extensive disease received amphotericin B in the combination of either itraconazole (2) or voriconazole (2) as shown in Table 3.

Table 3: Patients' clinical and laboratory profiles and treatment.

S. no.	Extrasinus extension	Histopathology result	Mycology result	Type of surgery	Antifungal / duration	Follow up duration	Treatment outcome
1	Nasopharynx	CGI + fungal hyphae	None	Endoscopic	Voriconazole for 3 months	Lost	
2	Orbital	CGI + fungal hyphae	None	Endoscopic	Itraconazole for 1 year	2 years	Remission
3	Frontal bossing	CGI + fungal hyphae	*A fumigatus*	Endoscopic	Amphotericin B+voriconazole for 3 months	12 months	Residual/ recurrence
4	Intracranial	CGI + fungal hyphae	*A fumigatus*	Endoscopic	Amphotericin B+itraconazole for 1 year	8 months	Residual/ recurrence
5**	Intracranial	CGI	*Candida*	Open	Amphotericin B+voriconazole for 1 year	6 months	Remission
6**	Intracranial	CGI	*A. niger*	Endoscopic	Voriconazole for 3 months	Lost	
7	Periorbital, infratemporal and pterygopalatine fossa	CGI + fungal hyphae	None	Open	Amphotericin B+itraconazole currently		Residual/ recurrence
8	Orbital	CGI + fungal hyphae	None	Endoscopic	Itraconazole for 8 months	24 months	Remission
9	Orbital	CGI + fungal hyphae	None	Endoscopic	Itraconazole for 1 year	18 months	Remission
10	Intracranial	CGI + fungal hyphae	None	Open	Voriconazole for 9 months	15 Months	Remission

CGI =Chronic granulomatous inflammation. The patient with frontal bossing declined open frontal sinus surgery. **Patient 5 and 6 had positive culture though fungal hyphae were not seen on histopathology.

Table 4: Summary of treatment and outcome.

Treatment outcome	Type no	Disease extent			Type of surgery		*Antifungal treatment			
		Sinonasal	Orbital/ nasopharynx	Intracranial/ infratemporal fossa	Endoscopic	Open	A	B	C	D
Remission	5		3	2	3	2	3	1		1
Residual/ recurrence	3			3	2	1			2	1
Lost to follow up	2	1	1		2			2		
Total	10	0	4	6	7	3	3	3	2	2

*A =itraconazole, B =voriconazole, C =itraconazole + amphotericin B and D =voriconazole + amphotericin B. All the patients that had residual disease had extensive disease at presentation. There was remission of disease in 3 patients that received Itraconazole alone.

Complete remission was achieved in 5 (50%) of the patients while 3 (30%) of the patients had a residual disease and 2 (20%) were lost to follow up (Table 4).

DISCUSSION

There is a paucity of published data on CGIFRS in Sub-Saharan Africa. Most reports on CGIFRS emanated from Sudan, India, Saudi Arabia and Pakistan. Similar to previous reports on CGIFRS, all ten patients in our study were immunocompetent.[4,5] The predominant age bracket of the patients in this study was 35 to 49 years; this is consistent with published data.[16,17]

While the mean duration of symptoms before presentation to our center in this study was 3.5 years (42 months), other studies reported between 1.5 to 2 years.[4,18,19] The factors responsible for the delay in diagnosis included late presentation caused by a preference for alternative therapy by traditional medical practitioners and complementary care from churches and mosques, limited access to specialist care in resource-challenged West African communities, financial constraints (patients pay from pocket for care in most Sub-Saharan communities), the non-specific clinical presentation of the disease and the high cost of investigations required for diagnosis.

The clinical presentations in our study are similar to previously reported cases.[17-20] Unilateral proptosis 80% was the commonest presenting symptom followed by nasal mass 70% (Table 1). Unilateral proptosis has been noted by various studies as one of the commonest presentations of CGIFRS.[6,18,20] Milosev et al in 1969 reported aspergillosis of the paranasal sinuses as the commonest cause of non-congenital unilateral proptosis in Sudan.[20] Nasal polyp was noted as the commonest mode of presentation of paranasal aspergillosis in immunocompetent Sudanese patients by Yagi et al and by Mahgoub et al.[16,18] Background chronic rhinosinusitis was only noted in 50% of our patients. An uncommon presentation noted in our study was a case of frontal bossing caused by the expansion of the anterior frontal sinus plate bilaterally (Figure 1A). Most patients presented in advanced disease stages with symptoms of invasion such as proptosis, cheek swelling with skin involvement and frontal bossing (Figures 2A and 3A). Invasion of paranasal sinuses was noted on the CT scan in all the patients mostly the ethmoid sinus (80%) followed by maxillary sinus and frontal sinuses 50.0% each (Table 2). This is consistent with findings in other studies.[4,17,19] Bone destruction 100%, intra-orbital extension (70.0%) and intracranial extension 50.0% were also noted on CT scan giving credence to the late stage presentation of most of the patients. Bone destruction has been noted in the published literature as very common.[12,13] Misdiagnosis was a major issue of concern. Most cases were reported radiologically as mitotic lesions based on the presence of bony destruction (Figures 2C and 3D). Differentiating mitotic lesions from CGIFRS by radiologic findings can however be difficult especially when the experience is lacking.

Positive histopathologic diagnosis was recorded in 80% of the patients. The initial cases were reported as chronic granulomatous inflammation with tuberculosis as a major differential. This resulted in repeated testing and delay in the commencement of treatment. It has been noted in the literature that CGIFRS has been misdiagnosed clinically, radiologically and pathologically as malignant neoplasms, sellar/ parasellar tumors, syphilis, tuberculosis, sarcoidosis, Wegener's granulomatosis, lymphoma, inflammatory pseudotumor, myospherulosis, mucopyocele, allergic fungal rhinosinusitis, and rhinoscleroma.[5,21-23] Heightened index of suspicion, use of special staining and improved experience for fungal hyphae detection positively resolved this challenge and resulted in increased diagnosis.

Fungal culture was positive in only 40% (4/10) of the patients, two of whom did not have positive fungal hypha identification on pathology (Table 3). *Aspergillus* species was the most frequent species isolated in 75% of cases in this study which is similar to reports from Sudan, Pakistan and India. However, *Aspergillus fumigatus* was the commonest fungus isolated in our study

while *Aspergillus flavus* was absent (Figure 1C). This is in contrast with previously published reports on CGIFRS showing *A. flavus* as the predominant species.[1,6] This result is similar to the reports from North America and America where *A. fumigatus* has been reported as the causative agent of CGIFRS.[6,24] The reason for the absence of *A. flavus* in this study could be attributed to possible wrong identification of the isolated fungus and will require further studies with advanced diagnostic techniques.

Figure 1: (A and B) Pre and post antifungal treatment photographs of patient with frontal bossing, (C) slide of *A. fumigatus* cultured from the patient.
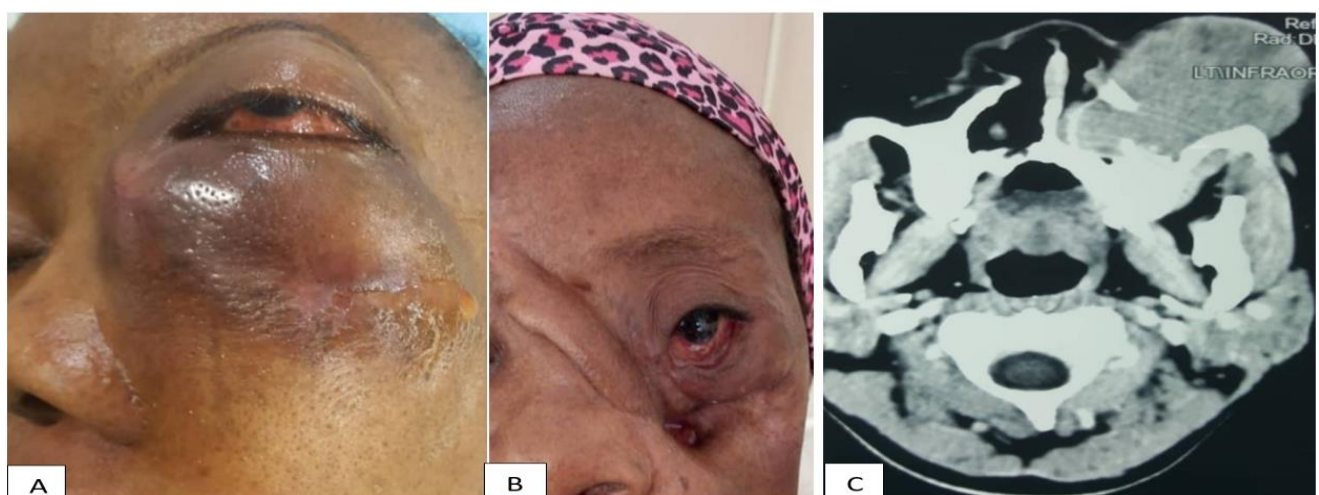
Figure 2: (A and B) Pre and post-surgical treatment photographs of patient with CGIFRS involving the left maxilla having a persisting discharging sinus, (C) axial view CT scan at presentation showing destruction of the maxilla and disease extension into the infratemporal fossa and pterygoid fossa.

All the patients had surgical excision (endoscopic in 7 patients and open in 3 patients) of fungal lesions with the opening of the ventilation channels of the sinuses. The type and extent of the surgery were dependent on the anatomic sites involved and the extent of the disease. The aim of the surgery was a complete removal of all infected tissue with the fungal elements. Repeat surgery when needed was not possible in 5 of 6 patients because of financial constraints.

All the patients had post-surgery antifungal medical treatment. Total remission was achieved with antifungal treatment in five patients, two of whom had extensive disease (Table 4) There is no adopted protocol for the treatment of CGIFRS in the country. Choice of first line antifungal drug was based on cost and availability. Amphotericin B was recommended as part of first line treatment to 6 patients with extensive disease but only 4 patients could afford it. Most patients started their treatment with Itraconazole which was affordable and readily available. Some were changed to Voriconazole due to poor response. Treatment with Voriconazole was mostly disjointed due to its high cost and sometimes non-availability. The two patients that were lost to follow up were on voriconazole. Residual disease was noted in 3 patients all of whom had extensive disease (intracranial

and infratemporal fossa extension) at presentation (Table 4). Seddiqui et al observed the poorest prognosis in patients with intracerebral extension followed by those with intracranial disease and best prognosis in patients with paranasal and orbital extension.[25] The reasons for residual disease in this series could be attributed to late presentation with extensive disease, delayed surgery, financial constraints that led to non-compliance to first choice antifungal agents and limited number of surgeries. Treatment outcome from the usage of different antifungals could not be compared due to the few number of patients involved in this study. Complete remission was achieved with Itraconazole in 3 patients that had intraocular extension of the disease. Gumaa reported complete remission of CGIFR in 12 out of 19 patients and good response in patients that had craniocerebral Aspergillosis with Itraconazole.[24] Excellent results have also been reported with Voriconazole.[25,26] All stages of

CGIFRS do well with Azoles but Voriconazole has the advantage of good cerebrospinal fluid penetrance.[29] Combination therapy of Amphotericin B and the Azoles gives a better result than single therapy.[1,30] The Azoles give better result as single agent treatment than Amphotericin B and should be used as first line drugs.[31] Suggested treatment protocol for chronic granulomatous fungal sinusitis by Rupa include excisional surgery plus itraconazole or voriconazole for stages 1 and 2 diseases, excisional or debulking surgery plus Voriconazole for stage 3 disease. Stage 1 disease is a disease limited to the nose and paranasal sinuses, an extension to orbit, palate and oral cavity stage 2 while intracranial, pterygopalatine and cheek extension is stage 3 disease.[31] No death has so far been recorded in this series. Clancy reported 15% and 44% mortality in patients with cranial and intracranial extension of the disease respectively.[19]

Figure 3: (A) Photograph at first presentation, (B) recurrence (post-surgery-external frontoethmoidectomy plus 6 months treatment with itraconazole), (C) post-treatment with amphotericin B and voriconazole, (D) coronal view CT scan at recurrence showing intracranial extension of disease, (E) slide of *Candida albicans* isolated from the patient.

CGIFRS may not be a rare disease in Nigeria. The diagnosis requires a high index of suspicion, meticulous clinical evaluation with a combination of histopathologic and mycologic diagnostic studies. Nasal mass and unilateral proptosis are the commonest clinical presentations in our series. *Aspergillus* species is the predominant causative organism. Combination of surgery with antifungal therapy is still the treatment of choice. Early diagnosis, adequate treatment with good outcome demands multidisciplinary collaboration and team efforts involving the radiologist, pathologist, mycologist, neurosurgeon and otorhinolaryngologist. There is an urgent need for the development of a national protocol for the management of CGIFRS and fungal infections in general. Efforts should be channeled towards identification and characterization of fungal species to aid application of protocols in cases where susceptibility to certain antifungals are already known.

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