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Chronic invasive fungal rhinosinusitis and granulomatous invasive fungal sinusitis: A systematic review of symptomatology and outcomes☆

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ABSTRACT

Introduction: Chronic invasive fungal rhinosinusitis (CIFRS) and granulomatous invasive fungal sinusitis are two uncommon diseases differentiated primarily by the pathologic finding of non-caseating granulomas in GIFRS. Both share many similarities in presentation. We aim to characterize the symptomatology and outcomes of these diseases.

Methods: A comprehensive search strategy was designed to identify studies in the Cochrane, EMBASE and PubMed databases from database inception to January 2022. Inclusion criteria included all patients with a diagnosis of either CIFRS or GIFRS. All studies were screened by two reviewers. Chi-square analyses were used where appropriate.

Results: 51 studies were included totaling 513 patients. The majority were diagnosed with CIFRS (389, 75.8 %) compared to GIFRS (124, 24.4 %). CIFRS was more common in immunocompromised or diabetic patients ($p < 0.0001$; $p = 0.02$). Patients with CIFRS were more likely to exhibit nasal symptoms including discharge ($p = 0.0001$), obstruction ($p = 0.03$) and congestion ($p = 0.001$) as well as systemic symptoms including fever, which no GIFRS patient exhibited, facial pain ($p = 0.007$), headache ($p = 0.004$). Aspergillus was the most common organism identified in both groups with a slight predominance among GIFRS patients ($p = 0.01$). GIFRS patients were also more likely to present with no identifiable organisms ($p = 0.0006$). CIFRS patients were more likely to die of disease ($p = 0.0008$).

Conclusions: CIFRS generally presents with more symptoms and is associated with poorer outcomes primarily occurring in an immunocompromised population. GIFRS likely follows a more insidious course in immunocompetent patients. Understanding the key differences in symptomatology and outcomes for these two populations is critical for appropriate diagnosis and prognostication.

1. Introduction

Fungal disease of the nose and paranasal sinuses encompasses a wide range of presentations. A classification schema proposed by deShazo in 1997 and adapted by Rupa et al. in 2022 groups fungal rhinosinusitis into three categories: invasive, non-invasive and mixed [1,2]. Within these groups there is high variability as acute invasive fungal sinusitis is a rapidly progressive, life-threatening disease that occurs primarily in immunocompromised patients, such as those on chemotherapy or with diabetes. Treatment for this condition is primarily surgical and carries high morbidity and the mortality even after treatment. Chronically invasive disease is rarer and divided into two categories based on histopathologic findings: granulomatous and non-granulomatous. Chronic invasive fungal sinusitis (CIFRS) and granulomatous invasive fungal sinusitis (GIFRS) follow a different disease course from acute invasive fungal sinusitis and are rare and the distinction between the two is not always clear [3]. The non-invasive category includes benign fungal diseases such as mycetoma (fungus ball) and allergic fungal sinusitis.

A 2009 consensus statement by the International Society for Human and Animal Mycology describes diagnostic criteria for fungal rhinosinusitis. Both CIFRS and GIFRS are categorized as having a time course of >12 weeks, whereas acute invasive fungal sinusitis has a time course of

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4 weeks or less [4]. However, the distinctions between CIFRS and GIFRS, beyond histopathological findings of granulomas in GIFRS remained a notably unresolved issue in this statement. Thus while these disease processes have different names, their behavior shares many similarities.

In this systematic review, we aim to characterize these disease entities, provide an understanding of epidemiology and symptomatology as well as determine if these two disease states are truly differing entities.

2. Methods

This systematic review was conducted in accordance with the recommendations of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses).

2.1. Search strategy

A comprehensive search strategy was designed and executed in Cochrane, EMBASE and PubMedfor results published from database inception through January 1, 2022. The search strategy utilized several search strings with controlled vocabulary to capture as many studies relating to CIFRS and GIFRS as possible.

2.2. Eligibility criteria and study selection

Studies that included patients with a clinical diagnosis of chronic invasive fungal rhinosinusitis or granulomatous invasive fungal sinusitis were included. We did not exclude patients based on age or gender. Given the relative rarity of this disease, to capture as many patients as possible, we did not require pathologic specimens or reporting of specific symptoms to be eligible for this study. Study selection was conducted independently by two separate reviewers, and only studies that were deemed eligible by both reviewers were included. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) Guidelines were used in study selection and review and is reported in Fig. 1.

3. Results

After dual review and exclusion, 51 studies and 513 patients were included. A diagnosis of CIFRS was three times as common as GIFRS (389, 75.8 % vs 124, 24.2 % respectively). There was a slightly higher percentage of men in the GIFRS group compared to the CIFRS group (67.7 % vs 56 %). This is included in Table 1. The most common countries in the CIFRS group were China, Pakistan, USA, India. The most

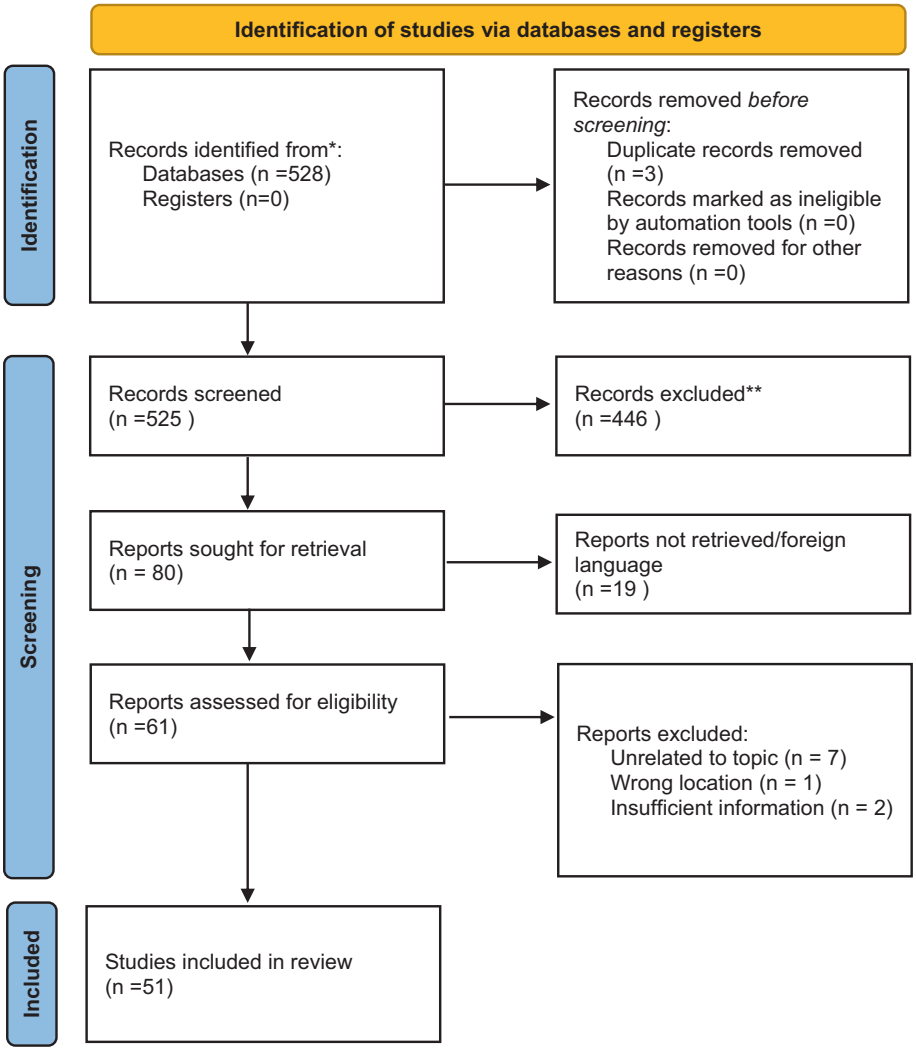

Fig. 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: https://doi.org/10.1136/bmj.n71.
For more information, visit: http://www.prisma-statement.org/.

Table 1
Demographic information and symptomatology of patients with CIFRS and GIFRS. Bolded p-values were significant using an alpha level of 0.05.

	CIFRS	GIFRS	
n	389	124	513
Male	221 (56.8)	84 (67.7)	
Female	168 (43.2)	40 (47.6)	
Average age (years)	56	47	
			p-value
Immunocompromised	86 (22.1)	4 (3.2)	**<0.00001**
Diabetes	101 (26.0)	20 (16.1)	**0.02**
Prior rhinologic conditions	6 (1.5)	8 (6.5)	**0.004**
Average duration of symptoms (months)	6.47	7.05	–
Nasal discharge	64 (16.5)	4 (3.2)	**0.0001**
Nasal obstruction	72 (18.5)	13 (10.5)	0.3
Congestion	44 (11.3)	2 (1.6)	**0.0009**
Parosmia/Parageusia	10 (2.6)	1 (0.8)	**0.2**
Visual changes	85 (21.9)	19 (15.3)	**0.1**
Visual loss	24 (6.2)	(6.5)	0.92
Proptosis	67 (17.2)	39 (31.5)	**0.0008**
Fever	22 (5.7)	0 (0.0)	–
Headache	124 (31.9)	23 (18.5)	**0.004**
Facial pain	112 (28.8)	15 (12.1)	**0.0001**
Altered mental status	2 (0.05)	3 (2.4)	0.61
Focal neurologic deficit	46 (11.8)	15 (12.1)	0.96
Mortality during follow up	45 (12)	2 (2)	**0.0008**
Alive with disease during follow up	44 (11)	9 (7)	0.2
Average duration of follow up (months)	23.8	13.26	–
Average number of surgeries	77	22	–

common countries in the GIFRS group were India, Pakistan, China and the USA. The most common countries overall were China, India and Pakistan (Table 2).

CIFRS was significantly more common in immunocompromised or diabetic patients ($p < 0.0001$, $p = 0.02144$). Patients with CIFRS were more likely to exhibit nasal symptoms including discharge ($p = 0.00014$), obstruction ($p = 0.033$) and congestion ($p = 0.0009$) as well as systemic symptoms including fever, which was not reported in GIFRS patients, facial pain ($p = 0.0065$), headache ($p = 0.0035$). On the other hand GIFRS patients were more likely to present with proptosis ($p = 0.0008$). Information on symptomatology is presented in Table 2. CIFRS patients were noted to have a higher mortality rate ($p = 0.00075$).

Aspergillus was the most common organism identified in both groups with a slight predominance among GIFRS patients ($p = 0.013$). GIFRS patients were also more likely to present with no identifiable organisms ($p = 0.00059$). CIFRS patients were more likely to die of disease ($p = 0.00075$) (Table 3) The average duration of treatment in the CIFRS group was 6.5 months and the average length of treatment in the GIFRS group was 9.1 months. The majority of patients were treated with a combination of endoscopic sinus surgery and systemic antifungals including voriconazole and amphotericin B. The average number of surgeries in the CIFRS group was 1.44 compared with 1.23 in the GIFRS group.

Table 2
Study location frequency by disease type.

Study location	CIFRS	GIFRS	Total
China	121	11	132
India	40	65	105
Pakistan	58	24	82
USA	56	9	65
Saudi Arabia	22	7	29
Korea	20	8	28
Italy	21	0	21
France	5	0	5
Japan	4	0	4
Germany	4	0	4
Turkey	4	0	4
Iran	1	0	1
Portugal	1	0	1

Table 3
Frequencies of involved organisms in CIFRS and GIFRS. Bolded p-values were significant using an alpha level of 0.05.

	CIFRS	GIFRS	p-value
Aspergillus	171 (0.44)	71 (0.57)	**0.01**
Mucor	36 (9)	5 (4)	0.06
None	16 (4)	18 (15)	**<0.00001**
Other	46 (12)	5 (0.04)	**0.01**

4. Discussion

The first report of a patient with proptosis and granulomatous fungal involvement of the nose and paranasal sinuses was published in 1967, yet in the most recent consensus statement the distinction between CIFRS and GIFRS remained controversial. There is a distinction between CIFRS and GIFRS on a histopathological basis, however the clinical distinction is less obvious [5,6]. Thus controversy remains if these are truly separate entities or part of a variable spectrum of disease presentation. However, the rate of diagnosed cases has been increasing over time [5]. Moreover, the subacute presentation and varying symptomatology between disease states makes these diseases a diagnostic challenge. Imaging and symptoms may mimic other conditions such as lymphoma or squamous cell carcinoma, or even other unrelated fungal disease states such as fungus ball [7–9]. As a result, patients may undergo treatment for unrelated disease states, delaying timely treatment of these conditions, which can lead to increased morbidity and mortality [10].

4.1. Epidemiology and patient characteristics of CIFRS and GIFRS

GIFRS is a rarer phenotype compared to CIFRS, with about a quarter of patients with invasive fungal disease demonstrating granulomas both in our study and in previous work [11]. Traditionally, CIFRS and GIFRS has been predominantly seen in countries with hot and dusty climates such as the Middle East, North Africa and Asia [1,2,4,12]. In general this was true of our population, however we noted that in the CIFRS population, the United States was the third most common country. This could represent increased immigration trends to the United States from involved countries in recent years and also reflects the insidious nature of this disease process as many patients may go months or years before being accurately diagnosed and treated. Regardless, it is important for clinicians to be aware of these disease states as it is not a condition limited to Asian and African countries.

Our results demonstrate that CIFRS is more commonly found in immunocompromised and diabetic patients while GIFRS is a disease of immunocompetent patients. Much of the literature supports this however it is not exclusive to either population [10,13–18]. Our results support the concept that CIFRS is primarily seen in immunocompromised and diabetic patients, as well as in an older population. HIV is less commonly a predisposing factor in the recent years, following the widespread availability of ART, but should be considered by clinicians as well [19]. No discrete exposures have been linked to either CIFRS or GIFRS. The prevalence in countries with hot and dusty climates suggests that dust and environmental fungus exposure may predispose patients to CIFRS or GIFRS. Additionally intranasal drug use and greenhouse farming have been reported as exposures in association with the development of CIFRS or GIFRS [16,20].

4.2. Symptomatology and outcomes

Possibly owing to its propensity to manifest in patients with immunocompromised status, CIFRS generally presents with higher symptom burden compared to GIFRS. In our review and analysis, CIFRS patients presented with significantly higher nasal symptoms and systemic symptoms. This may in part be attributed to their subdued immune

status allowing for increased disease manifestation. Local tissue damage, such as secondary to intranasal drug use, may be another vulnerability to the development of CIFRS [20]. Atypical expansion patterns and areas of involvement may also be noted in immunocompromised patients with CIFRS [7]. Notably, no GIFRS patients were reported to have fever, whereas 22 CIFRS patients had a recorded fever. Though reports exist of visual changes including orbital apex syndrome and cavernous sinus syndrome in patients with CIFRS and GIFRS, we found no difference in rates of visual changes between the two groups [18,21]. Proptosis is a commonly reported symptom among patients with GIFRS, which we noted in our review, and may be a reflection of a longer, more indolent disease process (Bakshi 2020) [1,10,23]. Interestingly, it has also been seen as a common symptom among patients with allergic fungal sinusitis [24].

GIFRS patients were also treated for longer, which may reflect a more persistent disease state, or it may be related to the fact that CIFRS patients had a higher mortality rate limiting treatment duration. Both CIFRS and GIFRS patients had similar levels of surgical interventions; endoscopic sinus surgery was the overwhelmingly most common approach. The combination of voriconazole and endoscopic sinus surgery is a commonly used and an effective treatment, though the duration of voriconazole therapy must be for several months [8,12,14,25]. Rupa et al. proposed a protocol for management of GIFRS based on a staging system they developed where early stage disease would be treated with a combination of voriconazole and endoscopic excision [26]. Conservative approaches are generally favored over radical approaches for early- and mid-stage disease and voriconazole is favored over the use of amphotericin B or itraconazole, with several reported cases of successful treatment of invasive disease even with extranasal extension [26–30]. For intracranial disease, treatment strategies generally avoid large, morbid, disfiguring resections given the utility of voriconazole as an adjunctive treatment. Endoscopic sinus surgery is still a mainstay to widely debride intranasal disease. Disease of the skull base can potentially be addressed via a combined approach, though the role of skull base resection has not been studied in detail. Ultimately, treatment strategies should be tailored to disease extent and speed of progression, with localized disease responding well to surgical treatment alone and voriconazole a useful adjunct [14,31].

Fungal involvement of the nose and paranasal sinuses commonly involves Aspergillus, Mucor, Rhizopus and Candida species, though it is not exclusive to these organisms [17,32–36]. Aspergillus was the most common fungus isolated in both groups; in prior studies it may be responsible for about 83 % of all cases of CIFRS [14]. Aspergillus is characterized on histopathology by septate, acute angle branching hyphae and may be accompanied by varying levels of inflammatory infiltrate in invasive states [37]. Mucormycosis and Rhizopus were two other fungus isolates that were more commonly seen in the CIFRS group, but this difference was not statistically significant. However, it follows that these two species have higher prevalence in a group with higher rates of immunocompromised patients. Reflected in our results is the concept that GIFRS tends to present with infrequent hyphal forms compared to CIFRS [6]. Thus, GIFRS may represent a state of prolonged inflammation even in absence of identifiable organisms, or after the fungus has been cleared from the body. However, even CIFRS may present without identifiable fungal forms [38]. Large biopsies may be required to provide enough material to identify sparse fungal elements [9]. PCR testing of sampled tissue is also another method to identify a causative organism in the absence of forms on histopathology [38]. Beta-D-glucan assays measure a component of the fungal cell wall (1,3-Beta-D-glucan) which is released in peripheral blood, and have been considered as a potential alternative to detecting fungal involvement compared with invasive biopsies. However, their role may be limited given low sensitivity and inability to differentiate between fungal species [39].

Additionally CIFRS patients had higher mortality rates than GIFRS patients, though their underlying comorbidities may be a large factor in this given prior studies showing associations between increased absolute neutrophil count and decreased mortality rate [40,41]. However, it is critical to identify these patients early so as to not delay diagnosis and treatment; intracranial spread can still occur in both forms of the disease and carries high mortality rates [22,28,42,43]. Other studies have placed mortality rates for CIFRS at 25% [44]; our review demonstrated a lower mortality rate at 11.6 % though this is subject to reporting bias. Though mortality rates are lower, morbidity may still be quite high as patients may continue to have sequelae of disease including vision loss [45].

4.3. Imaging findings

Imaging findings can vary among CIFRS and GIFRS patients and the patterns of erosion and extension into surrounding structures can mimic other disease states such as cancer or other infections [46]. The most common findings are nonspecific with mucosal thickening and sinonasal opacification [14]. Bony sclerosis, erosion and mass formation with extra-sinus extension is also commonly seen [47,48]. Extension into adjacent regions including the pterygoids and orbit is common [49]. A sinonasal hypointense mass on T1 and/or T2 with septal enhancement or loss of contrast enhancement, and involvement of cavernous sinus, sphenoid sinus, and meninges strongly suggest late-stage CIFRS with intracranial extension [14,39,48,50,51]. However, signal intensity is somewhat variable and another study found intermediate-high signal intensities more common in patients with CIFRS and low signal intensities more common in GIFRS [46]. Diffusion restriction on DWI sequences may help identify mass forming patterns from diffusely infiltrative patterns [47]. This variability may suggest different patterns of inflammation between and within the two phenotypes of CIFRS and GIFRS. Pathologic facial fractures may result from otherwise atraumatic events as a result of weakening of the facial complexes and buttresses [52]. While CT is useful for screening of erosive changes, MRI has the highest sensitivity and specificity for invasive chronic fungal disease, particularly with intracranial extension [44,53].

4.4. Characterization

Attempts to categorize the fungal diseases of the nose and paranasal sinuses have been debated and controversial. Classically, histopathology has been the main deciding factor with GIFRS containing noncaseating granulomas with fungal elements, multinucleate giant cells in a background of inflammatory infiltrate and fibrosis, possible invasion into deeper tissues including bone without angioinvasion [1]. Hematoxylin and eosin staining is usually sufficient for diagnosis, but Grocott's methenamine silver (GMS) is helpful to identify distinct fungal elements. CIFRS contains invasive fungal elements without the presence of granulomas. The lack of clear distinctions between the disease states is a complicating factor. A case report exists of a conversion from allergic fungal sinusitis to chronic invasive fungal sinusitis, while another case demonstrates development of allergic fungal sinusitis after treatment for GIFRS, illustrating the overlap between the disease states [22,54]. Coexistence of disease processes has also been reported. Fungal ball may has been seen both coexisting and progressing to IFS, particularly in immunocompromised or elderly patients [55]. Allergic fungal sinusitis may exist in tandem with GIFRS, supported by the observation that patients with early GIFRS may display features of allergic fungal including allergic mucin with fungal hyphae in addition to invasive features and granulomas [45,56]. Another study reports a subset of patients who presented with symptoms in a subacute chronology without features typical of invasive fungal sinusitis (IFS) suggesting there may be an intermediate category of patients between IFS and CIFRS [57]. Overall, our results suggest that CIFRS presents with increased severity compared to GIFRS, which may be due to underlying immunocompromise allowing the fungal species to proliferate. The presence of granulomas may represent an individual's ability to mount an immune response to contain fungal organisms, resulting in the

pathology of GIFRS compared to hosts without robust immune responses who are more likely to present with CIFRS. This may also explain the difference in occurrence, as immunocompetent hosts are less likely to have fulminant disease. Genetic predisposition cannot be excluded, particularly given the significant geographic bias. While it is possible that these disease states may exist as distinct entities that occur concurrently, as has been previously suggested, the existence of significant overlap and progression suggests these are all components of a broader spectrum of fungal disease of the nose and paranasal sinuses. Further studies and treatment paradigms should focus on these diseases as different points along a continuum.

5. Conclusions

CIFRS and GIFRS are two disease processes with varying symptomatology and outcomes. In general, CIFRS tends to present more severely, in an immunocompromised or diabetic population. GIFRS, while less symptomatic is characterized by the presence of granulomas on histopathologic analysis and proptosis as a hallmark symptom. While they share many similarities in diagnosis and treatment, accurate characterization of these processes, and of the overarching spectrum of fungal disease of the nose and paranasal sinuses has been hotly debated. Given the many similarities and overlap, with differences in symptom severity, we suggest that CIFRS and GIFRS should be assessed as part of a much larger continuum of fungal involvement in rhinosinusitis, rather than discrete categories to create treatment paradigms for this group of diseases.

Declaration of competing interest

None.

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