

Validate the classification of fungal rhinosinusitis: A retrospective analysis of 162 patients at a single institution

1 | INTRODUCTION

In 1997, deShazo et al^{1,2} conducted a literature review and proposed a novel classification of fungal rhinosinusitis. The authors divided fungal rhinosinusitis into invasive and non-invasive forms. The classification included acute and chronic invasive fungal rhinosinusitis (AIFRS and CIFRS), chronic granulomatous fungal rhinosinusitis, fungus ball and allergic fungal rhinosinusitis (AFRS). Nowadays, the classification proposed by deShazo et al is widely accepted and is frequently cited in related studies. Classification of fungal rhinosinusitis is important to accurately predict the prognosis and choose an appropriate therapy. When deShazo et al initially developed the criteria in 1997, only 2 out of 30 cases belonged to the classification of CIFRS in his series: both were diagnosed after a protracted disease course lasting over 6 months, resulting in orbital apex syndrome and late neurological sequelae.²

Owing to the rising prevalence of fungal infection caused by better survival of immunocompromised hosts in the modern era, it is important to gain a better understanding of the characteristics of fungal rhinosinusitis. Therefore, the purpose of this study was to clarify the characteristics of fungal rhinosinusitis. Furthermore, we planned to validate the application of deShazo's classification for fungal rhinosinusitis in our patients. We conducted a retrospective chart review comparing patients with AIFRS, CIFRS and fungus ball in our institute. AFRS and granulomatous fungal rhinosinusitis are rare in Asian countries and therefore these two forms were not included in this study.

2 | METHODS

A retrospective chart review was conducted from 2004 to 2018. Study subjects were enrolled based on evidence of pathological or cultural evidence of sinonasal fungal infection. Clinical details including demographics, laboratory data, comorbidities, culture results and treatment outcome were retrieved from chart review. Classification of fungal rhinosinusitis was based on histopathology, host's immune status and clinical features according to the classification system proposed by deShazo et al¹. In brief, all AIFRS patients demonstrated both a fulminant infectious clinical course

(less than 4 weeks) and pathological evidence of angioinvasion by fungal hyphae or acute tissue necrosis. Patients with sinus fungus ball presented with endoscopic hyphae accumulation in an isolate sinus cavity and met the classification criteria for the non-invasive form, that is no clinical or pathological evidence of invasive fungal infection. Other than the aforementioned definitions, patients who had invasive sinonasal fungal infection were categorised as CIFRS.

2.1 | Ethical considerations

This study was approved by the institutional review board of Taichung Veterans General Hospital (approval number: CE18072A).

2.2 | Statistical analysis

Clinical data were represented in terms of frequencies and means. Statistical comparisons were performed using IBM SPSS Statistics for Macintosh, version 20.0 (IBM Corp., Armonk, NY, USA). Kruskal-Wallis test and Pearson's chi-squared test were applied whenever appropriate. A *p* value less than 0.05 was regarded as statistically significant.

3 | RESULTS

A total of 22 AIFRS patients, 30 CIFRS patients and 110 patients with sinus fungus ball were enrolled in this study. The characteristics of the study subjects are listed in Table 1. Patients with CIFRS were significantly older than the others (*P* = .021). Females are generally thought to be more likely to have sinus fungus ball. Nevertheless, males outnumbered females among AIFRS patients in our series. Several risk factors are well-known to be associated with IFRS including diabetes, haematological malignancy, anaplastic anaemia, bone marrow transplant, acquired immunodeficiency syndrome, chronic renal diseases, liver cirrhosis and use of immunosuppressant.^{3,4} In our results, all patients with AIFRS, 19 with CIFRS, and 36 with sinus fungus ball had known risk factors associated with fungal infection.

Patients with sinus fungus ball often presented with nasal symptoms such as nasal obstruction, rhinorrhea, fetid odour, epistaxis, hyposmia and sometimes complaint of facial pain or headache. Few fungus ball patients had no associated symptoms but had been

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diagnosed by imaging studies conducted for other conditions. In contrast, most CIFRS as well as AIFRS patients sought medical help for extra-sinonasal symptoms. Symptoms in CIFRS patients included fever, nasal obstruction, rhinorrhea, nasal bleeding, facial pain, headache, ptosis, diplopia and visual disturbance. Similar symptoms presented in AIFRS patients but with far more rapid progression compared with CIFRS.

Sinus fungus ball was usually localised unilaterally in a single sinus, mostly in the maxillary sinus. Nevertheless, fungal infection involved the septum, turbinates, palate or multiple sinuses in IFRS patients. Orbit involvement is frequently diagnosed in CIFRS patients. There was a higher incidence of central nervous system involvement in AIFRS patients than in those with CIFRS. Typical radiological characteristics of sinus fungus ball were calcified densities within the sinus, sclerotic sinus wall or dilation of sinus ostium. Although some CIFRS patients had dense hyphae accumulation in the sinus, notable dilation of the ostium was rare. Other CT or MRI features of IFRS included disease extension of soft tissue, bony destruction, meningeal enhancement, brain abscess or orbital cellulitis. Some representative images are shown in Figure 1.

In the histological evaluation, sinus fungus ball was characterised by accumulation of dense hyphae without fungal mucosal invasion. Acute or chronic inflammation caused by coexisting bacterial infection was frequently found. Polyps and mild tissue eosinophilia were noted in seven fungus ball patients. Nevertheless, their presentation did not fit the criteria of AFRS defined by deShazo's classification system (lack of peanut butter mucin and atopy).¹ Pathology of AIFRS showed angioinvasion of fungi, vascular thrombosis, infarction and necrosis, usually with scant inflammatory cells. CIFRS demonstrated transitional histological features between AIFRS and sinus fungus ball, which included: tissue necrosis, pyogranulomatous inflammation, osteomyelitis, chondritis or dense hyphae accumulation, often accompanied with inflammatory cell infiltration (Figure 2).

Only four fungus ball specimens demonstrated positive fungal culture results. Positive fungal culture was found in 46.7% of our CIFRS patients, whereas only one AIFRS patient had a negative fungal culture result. In our series, most IFRS were caused by *Aspergillus* spp. and others were infected with *Mucor*, *Candida*, *Fusarium*, or *Scheosporium* spp. The mortality rate of AIFRS was 54.5%. None of the CIFRS or fungus ball patients died of fungal infection. One CIFRS patient had stroke and died of pulmonary emboli 5 months after fungal infection. Nevertheless, some of the patients who survived IFRS had post-fungal infection neurovascular sequelae.

4 | DISCUSSION

In the present study, all patients with AIFRS, 63% of CIFRS patients and 33% of fungus ball patients had known risk factors associated with fungal infection. The differences in the proportions of immunocompromised subjects may explain why AIFRS leads to an aggressive clinical course, whereas sinus fungus ball infection has an indolent presentation. Sinus fungus ball infection in patients with risk factors

Key points

- Patients with AIFRS present with aggressive disease often extension to orbit or cranium. Pathology findings include angioinvasion of fungi, vascular thrombosis, infarction and necrosis. Most AIFRS specimens grow in laboratory fungal culture.
- Sinus fungus ball occurs to mildly immunocompromised or immunocompetent subjects. Fungus ball is characterised by accumulation of dense hyphae without mucosal invasion. Culture from fungus ball rarely grows.
- CIFRS is a disease entity comprising a transitional spectrum from AIFRS to sinus fungus ball.
- One form of fungal rhinosinusitis could evolve into another depending on the immunity status of the host.
- deShazo's classification for fungal rhinosinusitis is feasible for grouping patients, which may be useful for treatment decision-making and prediction of outcome.

may progress to IFRS if the immune system deteriorates.⁵ Five patients with AIFRS in this study transformed into a chronic fungal infection after restoration of the patient's immune function. In addition, fifteen of our CIFRS patients presented with dense hyphae in sinus similar to fungus ball (Figure S1). It has been reported that different forms of fungal infection could evolve from one form to another when the host's immunity status changes.⁶ AFRS is prevalent in western countries but is relatively rare in Asia. Patients with AFRS have type I hypersensitivity, nasal polyposis with allergic mucin within the sinus cavity, and present with thick mucus, nasal obstruction and anosmia.⁷ The presentation of AFRS could vary by geographic, genetic or ethnic factors. Seven fungus ball patients in this study presented with nasal polyps and mild tissue eosinophilia. Nevertheless, they were not atopic and were lack of typical peanut butter mucin. We presume that these subjects presented with transitional changes from fungus ball to AFRS.

Most of our IFRS patients sought medical help for extra-sinus symptoms. The orbital apex syndrome, a collection of cranial nerve deficits, is known to be associated with CIFRS. Five of our CIFRS patients had orbital apex syndrome. All of them had a protracted disease course, and two had been misdiagnosed as non-infectious orbital inflammatory condition. Unilateral disease was found in all but two patients with sinus fungus ball. Although unilateral predominance was seen in fungus ball and CIFRS, AIFRS tended to involve bilateral multiple sites. Septum and palatal involvement frequently resulted in septal perforation or oronasal/oroantral fistula. Typical radiological findings of sinus fungus ball are calcified density, sclerotic sinus wall or ostium expansion on CT images.⁶ Bony destruction and extension of disease beyond the confines of the sinuses were important in the clinical impression of IFRS but were non-specific for diagnosis. MRI is superior to CT for evaluation of soft tissue, orbit, meninges, cavernous sinus or brain.⁸

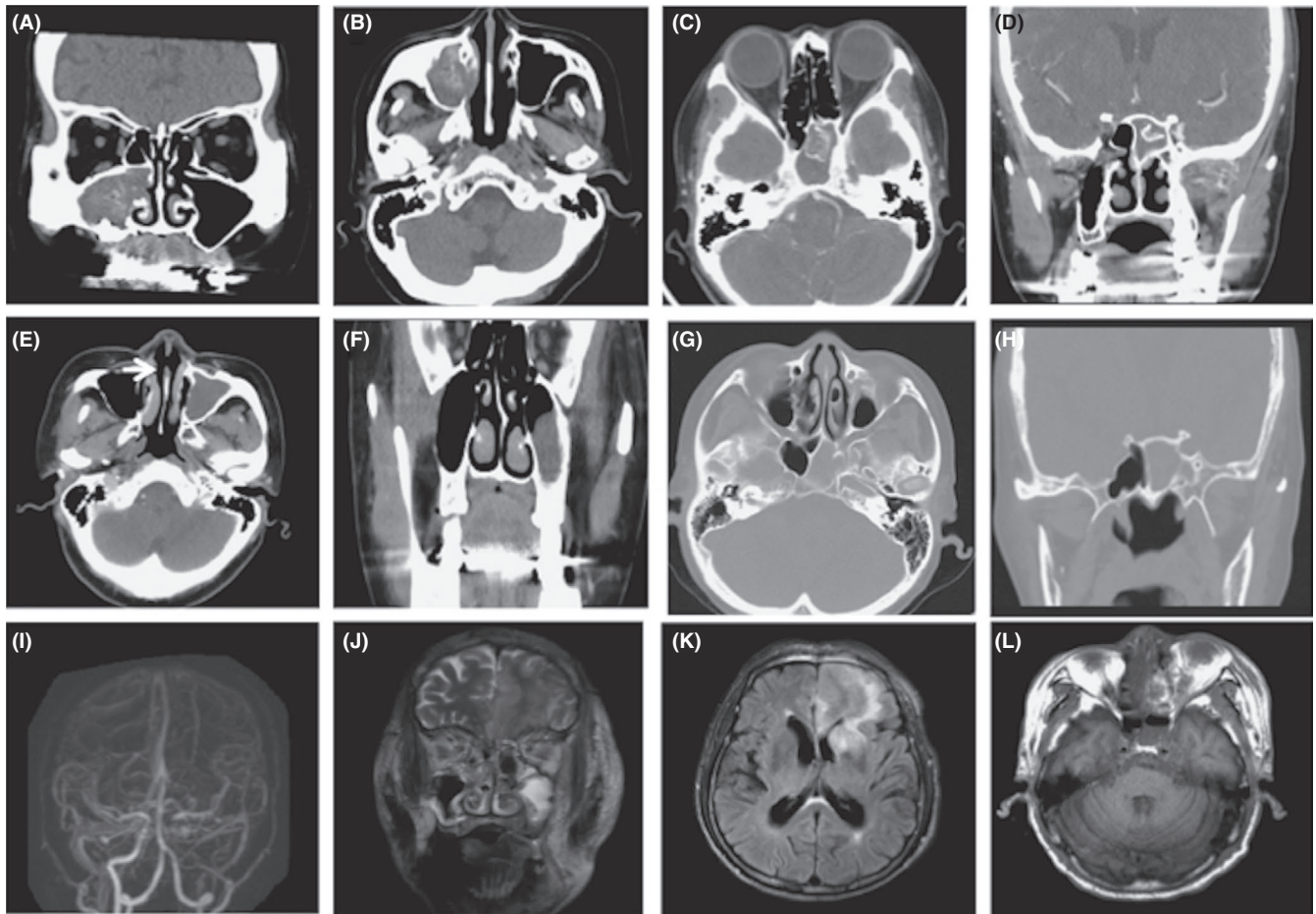


FIGURE 1 A 79-year-old female had experienced right maxillary fungus ball. She presented with fetid odour and frequent nasal bleeding. Her computed tomography (CT) scan revealed calcified density in sinus, sclerotic sinus wall and dilation of ostium of right maxillary sinus (A&B). Another 59-year-old female with bronchiectasis had been diagnosed with left sphenoid fungus ball. She presented with chronic headache for a long time. CT scan demonstrated calcified density, sclerotic sinus wall and expansion of sphenoid opening (C&D). A 55-year-old female had experienced chronic invasive fungal rhinosinusitis. She had diabetes and underwent treatment for acute myeloid leukaemia at that time. She presented with fever and bloody nasal discharge for one month. Physical examination found a septal ulcer. Her CT scan revealed a septal perforation (arrow) and left maxillary sinusitis. Though there was neither calcified density nor sinus ostium dilation, endoscopic surgery found dense hyphae accumulation within the left maxillary sinus (E&F). A 62-year-old female presented to the emergency room with right hemiplegia and severe headache. Her CT scan showed left sphenoid sinusitis and magnetic resonance angiography revealed left internal carotid artery occlusion (G, H&I). Sinus fungal cultures confirmed the diagnosis of *Aspergillus* CIFRS. A 70-year-old male presented with fever, ophthalmoplegia and conscious changes. He had diabetes and chronic renal disease. His magnetic resonance images revealed fungal infection with involvement of the sinus, orbit and cranium. Endoscopic sinus surgery confirmed the diagnosis of mucormycosis-related acute invasive fungal rhinosinusitis (J, K&L)

Although some CIFRS patients had dense hyphae accumulation in the sinuses, the typical CT features of fungus ball (calcified density, sclerotic sinus wall or ostium expansion) were not always seen on their CT images. A possible explanation is that impaired host immunity reduces the tissue modification from fungal infection.

In our results, 95.5% of AIFRS, 46.7% of CIFRS and only 3.6% of sinus fungus ball had positive fungal cultures. The aggressiveness of disease depends not only on local host factors and immune status, but also fungal virulence. The fungal culture rates could result from infection with differently virulent fungi among 3 groups. Several factors such as growth rate, thermotolerance, enzyme activity, and the ability to produce biofilm have been reported to be associated with

fungal virulence.⁹ AIFRS mostly caused by virulent fungi that were easy to grow in laboratory. Lack of viable fungi in sinus fungus ball explained why fungus ball culture rarely grew.⁵

The mortality rate of our AIFRS patients was 54.5%. There was no mortality from fungal infection in CIFRS patients in this case series. Nevertheless, late sequelae including diplopia, blindness, hemiplegia and oroantral fistula have severely impacted the quality of life of CIFRS survivors.

Kosmidis et al conducted a thorough review of published pulmonary aspergillosis studies and concluded that different forms of pulmonary aspergillosis should be viewed as a semicontinuous spectrum of disease and one form may evolve into another.⁶ We proposed that

TABLE 1 Characteristics of study subjects

Group	Acute invasive fungal rhinosinusitis N = 22	Chronic invasive fungal rhinosinusitis N = 30	Sinus fungus ball N = 110	P
Age, years (range)	57.8 (34-76)	64.4 (23-87)	56.8 (23-82)	0.021 ^{a,*}
Sex (M/F)	14/8	10/20	29/81	0.003 ^{b,*}
Risk factors (N)	None = 0 Yes = 22 ^c (Diabetes 11; haematologic malignancy 8; anaplastic anaemia 1; non-haematological malignancy 1; medical immunosuppressant 2; chronic renal diseases 2; liver cirrhosis 1)	None = 11 Yes = 19 ^c (Diabetes 14; haematologic malignancy 1; non-haematologic malignancy 2; medical immunosuppressant 3; chronic renal disease 2)	None = 74 Yes = 36 ^c (Diabetes 17; haematologic malignancy 1; non-haematologic malignancy 7; medical immunosuppressant 9; chronic renal disease 1; liver cirrhosis 1; bronchiectasis 2)	<0.001 ^{b,**}
Presenting symptoms (N)	Nasal obstruction (2) Rhinorrhea (2) Nasal bleed (1) Facial pain (5) Facial swelling (3) Ptosis (6) Visual loss (8) Headache (3) Limitation of eye movement (8) Fever (14) Conscious change (6)	Nasal obstruction (2) Rhinorrhea (6) Nasal bleed (3) Facial pain (7) Facial swelling (7) Headache (15) Ptosis (3) Visual loss, blindness (11) Limitation of eye movement (10) Orbital apex syndrome (5) Fever (6) Facial palsy (2) Delirium (1) Hemiplegia (1)	Nasal obstruction (41) Rhinorrhea (42) Post-nasal dripping (45) Fetid odour (17) Hyposmia (3) Nasal bleed (21) Facial pain (17) Facial swelling (2) Headache (13) Asymptomatic (4)	
Location (N)	Septum, turbinates (15) Palate (4) Sinus, unilateral (6) Sinus, bilateral (4) Orbit (8) Central nervous system (8)	Septum, turbinates (5) Palate (2) Sinus, unilateral (24) Sinus, bilateral (6) Orbit (13) Central nervous system (4)	Sinus, unilateral (108) Sinus, bilateral (2)	
Pathogen ^d (N)	<i>Aspergillus</i> spp. (11) <i>Mucor</i> spp. (9) <i>Fusarium</i> spp. (1) Undetermined (1)	<i>Aspergillus</i> spp. (24) <i>Candida</i> spp. (2) <i>Mucor</i> spp. (1) <i>Schistosporium</i> spp. (2)	<i>Aspergillus</i> spp. (104) Undetermined (6)	
Fungal culture (N, %)	No growth (1, 4.5%) Growth (21, 95.5%)	No growth (16, 53.3%) Growth (14, 46.7%)	No growth (58, 52.7%) Growth (4, 3.6%) Not done (48, 43.6%)	<0.001 ^{b,**}
Sequelae ^e (N)	Blindness (1) Septal perforation (2) Oronasal/oroantral fistula (3)	Diplopia (1) Blindness (6) Septal perforation (1) Oroantral fistula (2)	0	
Mortality ^e (N, %)	12 (54.5%)	0 ^f	0	<0.001 ^{b,**}

^aKruskal-Wallis test.^bChi-square test.^cSome patients had multiple risk factors.^dBased on hyphae morphology or culture results.^ecaused by fungal infection within 3 months after diagnosis.^fOne patient died of pulmonary emboli 5 months after diagnosis of fungal infection.

*P < .05.

**P < .01.

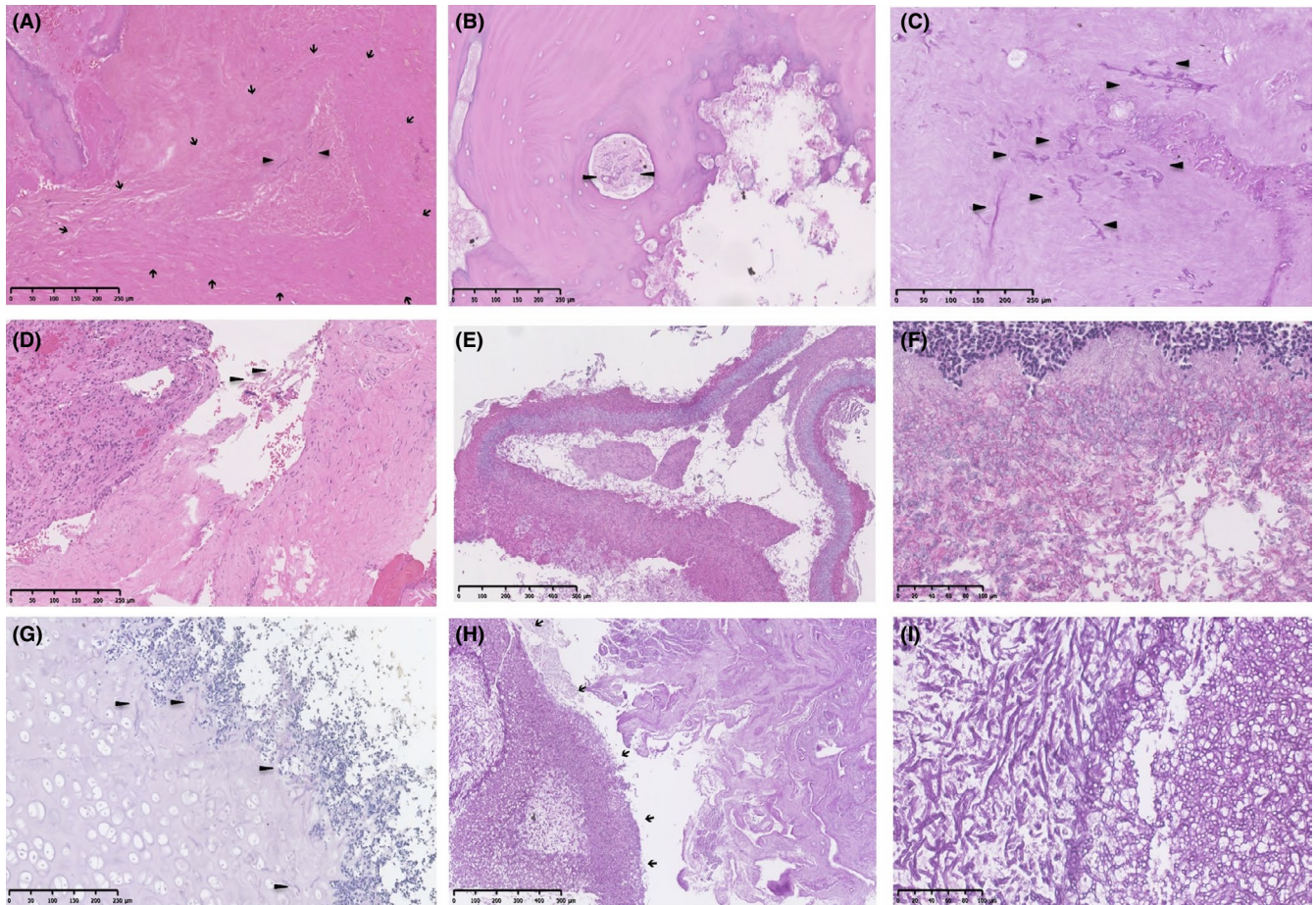


FIGURE 2 Representative histology photos of acute invasive fungal rhinosinusitis (A-C, mucormycosis) demonstrate widespread necrosis, fungal hyphae invading blood vessel, bone and soft tissue (A: Haematoxylin and eosin stain, black arrows mark the boundary of a blood vessel and arrow heads mark the hyphae within the blood vessel; B&C: Periodic acid-Schiff stain, arrow heads mark the hyphae in a bone trabeculae and soft tissue). Chronic invasive fungal rhinosinusitis (D-H, aspergillosis) resulted in chronic nasal inflammation, osteomyelitis and chondritis (D: H&E stain, hyphae found in inflammatory nasal tissue, marked with arrowheads; E&F: H&E stain, chronic osteomyelitis infiltrated with lots of hyphae; septate hyphae are demonstrated in high-power view; G: PAS stain, hyphae are identified in septum cartilage and marked with arrowheads). H: PAS staining of sinus fungus ball demonstrates dense aspergillus hyphae accumulation outside the sinus mucosa (arrows outline the fungus ball). I: Acute-angle septate hyphae are shown in a high-power view

sinonasal fungal infection demonstrates transitional changes between each classification and summarised our findings in Figure 3, which is very similar to aforementioned patterns of pulmonary aspergillosis.^{6,10}

5 | CONCLUSION

We validated the deShazo's classification with our patients with fungal rhinosinusitis and found this classification is feasible for grouping patients and predicting treatment outcomes.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTION

MWH and CYC: collection of data; CYW: data interpretation and pathology review; RSJ: manuscript writing; KLL: manuscript writing and final approval.

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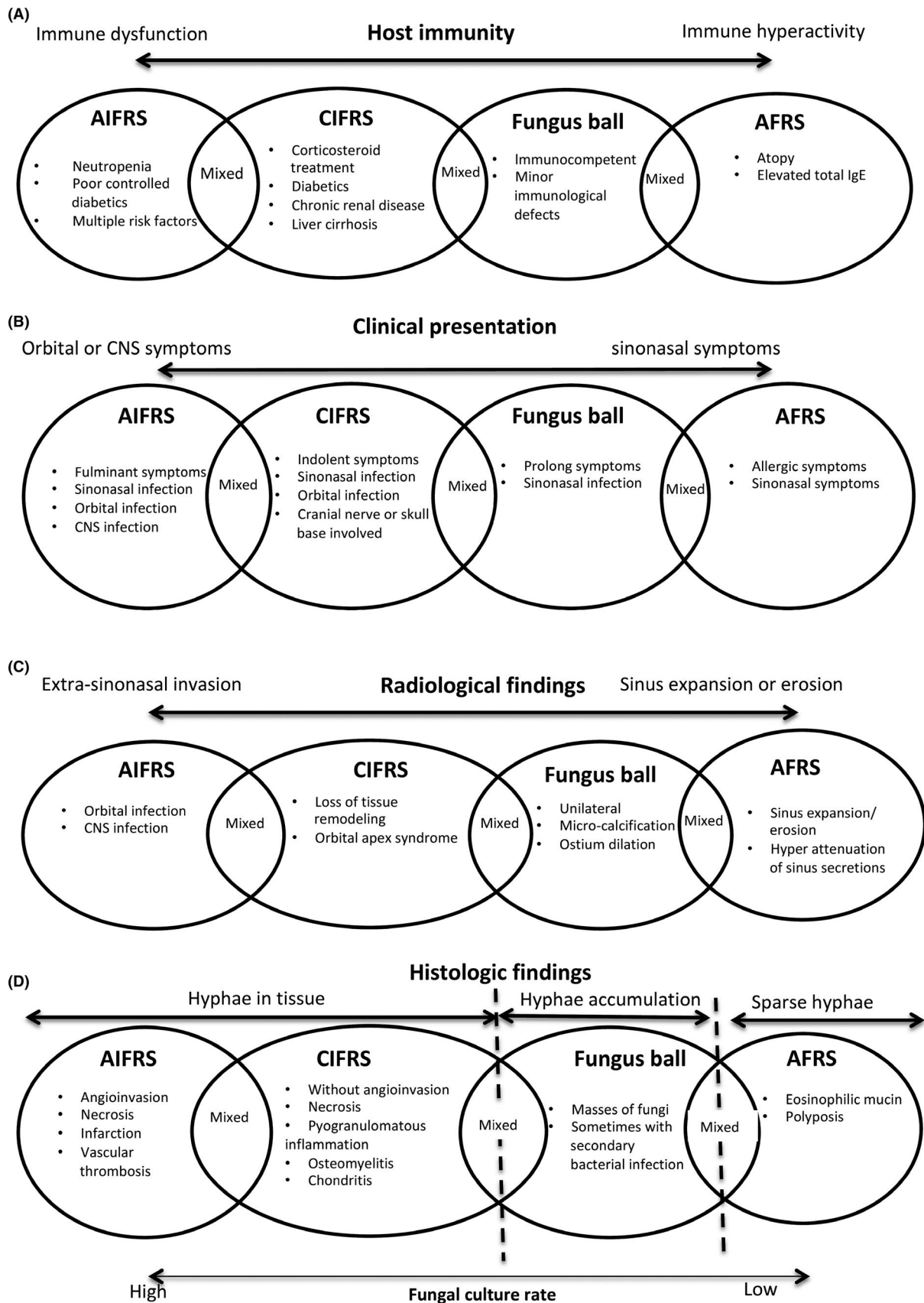


FIGURE 3 Clinical (A&B), radiological and pathological (C&D) features grouped according to deShazo's classifications for fungal rhinosinusitis

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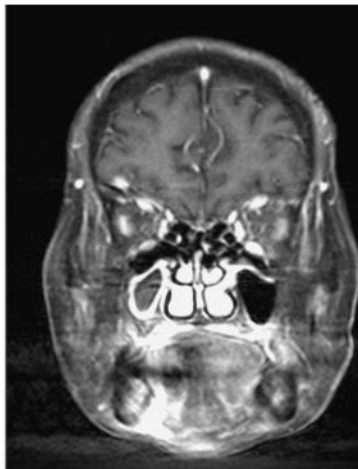
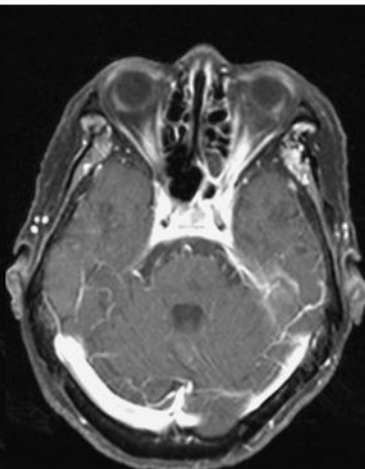
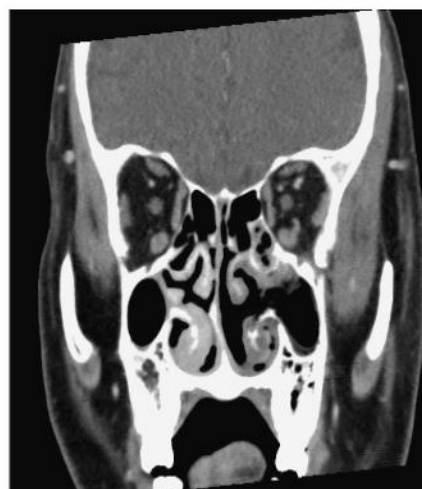
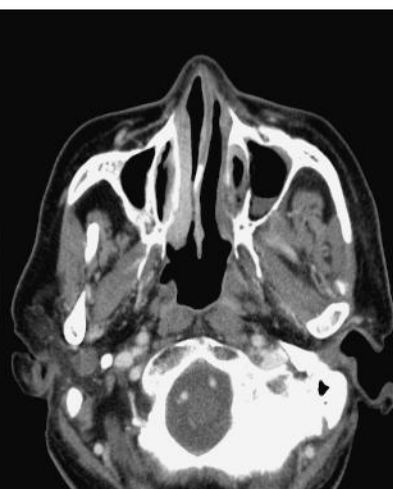
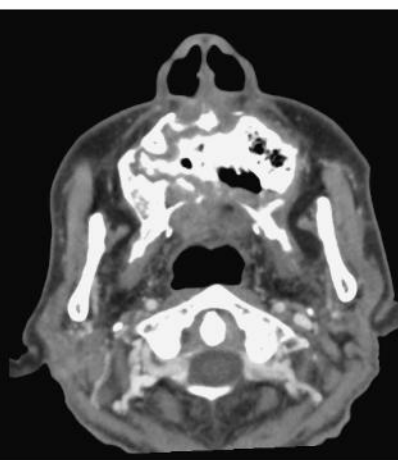
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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