Academia Open
Vol 10 No 1 (2025): June (In Progress)
DOI: 10.21070/acopen.10.2025.11466 . Article type: (Medicine)

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ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

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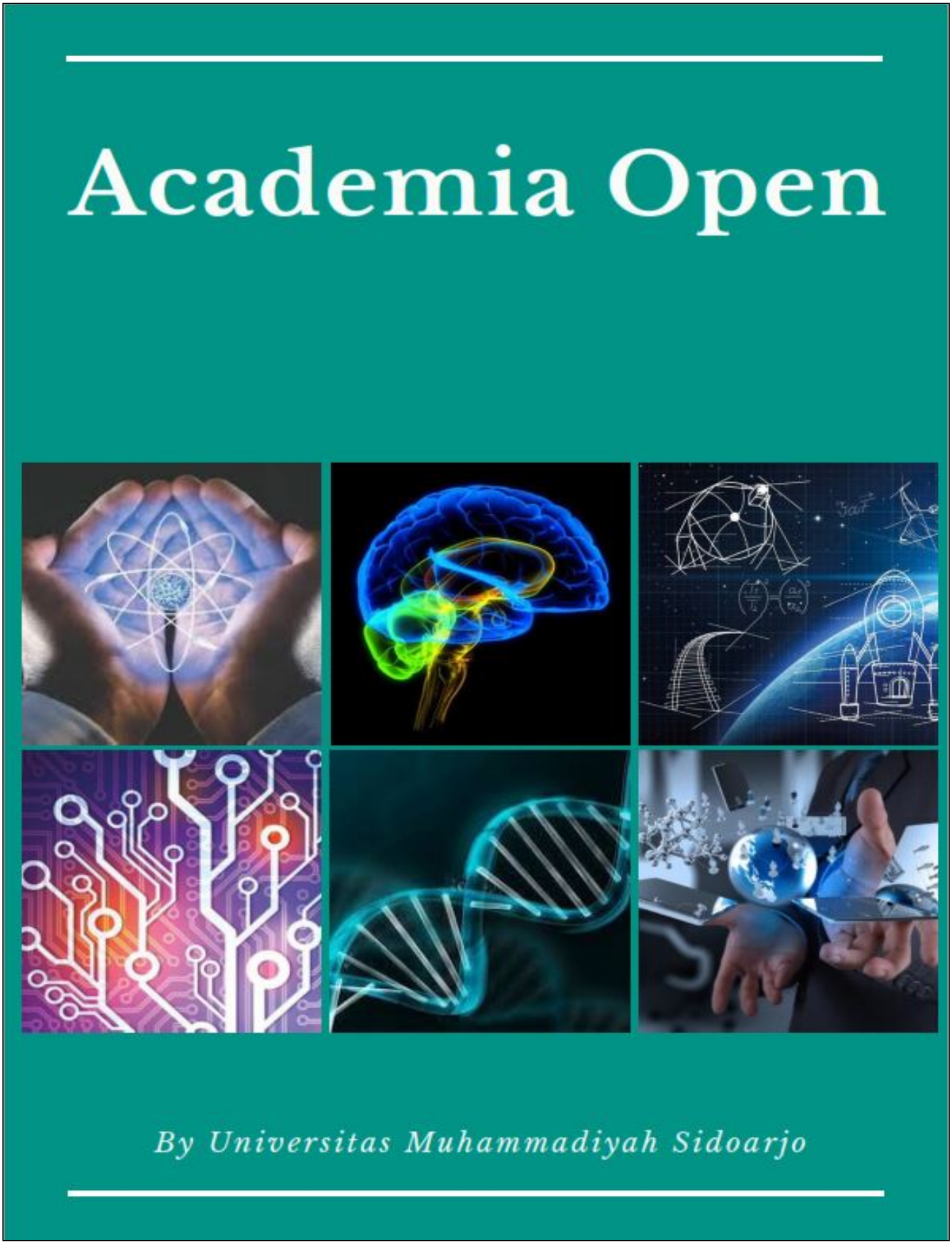

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ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

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Histopathological Features of Allergic Fungal Rhinosinusitis Provide Diagnostic and Therapeutic Insights

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Abstract

Background: Allergic Fungal Rhinosinusitis (AFRS) is a non-invasive subtype of fungal sinusitis marked by a hypersensitivity reaction to environmental fungi, predominantly Aspergillus. **Specific Background:** Its diagnosis depends on integrated clinical, radiologic, and histopathological assessments. **Knowledge Gap:** Despite established criteria, the histopathological profile of AFRS in Iraqi clinical settings remains underreported, limiting diagnostic precision. **Aim:** This study aimed to characterize the histopathological features of AFRS in patients managed at Al Salam Teaching Hospital, Mosul, Iraq, to improve diagnostic accuracy. **Results:** In a retrospective analysis of 42 cases from January 2023 to January 2024, all specimens demonstrated allergic mucin (100%), with 95.2% exhibiting dense eosinophilic infiltrates and 85.7% showing Charcot-Leyden crystals. Fungal hyphae, typically sparse, septate, and branching—consistent with Aspergillus—were detected in all samples using GMS and PAS stains. **Novelty:** This study highlights the consistent presence of Charcot-Leyden crystals in addition to the classical triad, emphasizing their diagnostic value in differentiating AFRS from other chronic rhinosinusitis forms. **Implications:** Recognition of these histopathological hallmarks is essential to guide treatment strategies focused on surgical and anti-inflammatory modalities, rather than systemic antifungal therapy.

Highlight:

- Consistent Triad: Allergic mucin, eosinophils, and fungal hyphae are key diagnostic features.
- Diagnostic Marker: Charcot-Leyden crystals enhance specificity in AFRS detection.
- Therapeutic Focus: Emphasizes surgery and anti-inflammatory therapy over antifungals.

Keywords: Allergic Fungal Rhinosinusitis, Histopathology, Charcot-Leyden Crystals, Eosinophilic Infiltrate, Aspergillus

Published date: 2025-06-25 00:00:00

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

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Introduction

AFRS AFS is a unique clinicopathologic entity that is a form of the non-invasive fungal sinus allergy that is caused by a Type I hypersensitivity reaction to colonizing airborne fungi [1]. It is the most prevalent type of fungal sinusitis, occurring in immunocompetent patients, usually adolescents and young adults [2]. Patients frequently become symptomatic with chronic rhinosinusitis symptoms of nasal obstruction, purulent rhinorrhea, head pressure, and large nasal polyposis, commonly unilateral [3] [4]. The full pathophysiology of AFRS is incompletely characterized but is thought to be an IgE-mediated inflammatory process that occurs in the setting of genetically susceptible patients and fungal antigens [5]. This intense allergic response leads to the accumulation of thick, tenacious, eosinophil-rich mucus, often termed "allergic mucin," within the paranasal sinuses. This mucin can cause significant sinus expansion and bony erosion through pressure effects, mimicking a malignant process on imaging [6] [7].

The diagnosis of AFRS is based on a set of criteria proposed by Bent and Kuhn, which include the presence of allergic mucin, characteristic radiological findings, positive fungal stain or culture from sinus contents, and the absence of tissue invasion [8]. While clinical and radiological features are highly suggestive, histopathological examination of surgically removed tissue remains the gold standard for confirming the diagnosis and, crucially, for excluding invasive fungal disease [9].

In Iraq, and specifically in Mosul, environmental factors such as dust storms and agricultural activities may contribute to a high burden of airborne fungal spores, potentially influencing the prevalence and presentation of AFRS. However, there is a paucity of local data characterizing the specific pathological features of this condition. Therefore, this study was undertaken to describe the classic and variant histopathological findings in patients diagnosed with AFRS at Al Salam Teaching Hospital in Mosul, aiming to correlate these features with diagnostic and therapeutic considerations.

Methods

A. Study Design and Setting

A retrospective, descriptive study was conducted at the Department of Pathology, Al Salam Teaching Hospital, a major tertiary care center in Mosul, Iraq. The study reviewed archival materials from January 1, 2023, to January 31, 2024.

B. Patient Selection

The study included all patients who underwent functional endoscopic sinus surgery (FESS) for chronic rhinosinusitis and whose postoperative histopathological examination confirmed a diagnosis of AFRS.

1. Inclusion Criteria: Patients with a confirmed histopathological diagnosis of AFRS, defined by the presence of allergic mucin containing fungal hyphae without tissue invasion.

2. Exclusion Criteria: Patients with other forms of fungal rhinosinusitis (e.g., mycetoma, chronic invasive sinusitis, acute fulminant sinusitis), bacterial rhinosinusitis, or sinonasal tumors. Patients with incomplete clinical or pathological records were also excluded.

C. Data Collection and Histopathological Examination

Clinical data, including age, gender, and presenting symptoms, were retrieved from patient records. Surgical specimens, consisting of sinus contents and mucosa, were fixed in 10% neutral buffered formalin. The tissue was processed using standard paraffin-embedding techniques. Sections of 4-5 micrometers thickness were cut and stained with Hematoxylin and Eosin (H&E). Special stains, including Grocott's Methenamine Silver (GMS) and Periodic acid-Schiff (PAS), were performed on all suspected cases to highlight fungal elements.

The slides were reviewed by two independent pathologists. The following histopathological features were recorded:

1. Allergic Mucin: Presence of laminated, eosinophilic, and necrotic mucinous material.

2. Inflammatory Infiltrate: Presence, density, and type of inflammatory cells, with a focus on eosinophils.

3. Charcot-Leyden Crystals: Presence of these slender, hexagonal, eosinophilic crystals, which are breakdown products of eosinophils.

4. Fungal Elements: Presence, morphology (septate/aseptate, branching angle), and distribution of fungal hyphae

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within the mucin.

5. Mucosal Changes: Features such as edema, goblet cell hyperplasia, and basement membrane thickening.

6. Tissue Invasion: Absence of fungal invasion into the submucosa, blood vessels, or bone.

D. Ethical Considerations

The study protocol was approved by the Institutional Review Board of Al Salam Teaching Hospital. As a retrospective study of anonymized archival material, the requirement for individual patient consent was waived.

Results and Discussion

A. Results

Characteristic	Number of Patients	Percentage (%)
Age Group (years)		
14–20	10	23.8%
21–30	18	42.9%
31–40	11	26.2%
41–45	3	7.1%
Gender		
Male	24	57.1%
Female	18	42.9%

Table 1. ***D emographic Characteristics of Patients with AFRS (n = 42)***

During the study period, 42 patients met the inclusion criteria. The demographic characteristics of the patients are detailed in Table 1. The age of the patients ranged from 14 to 45 years, with a mean age of 28.5 years. There was a slight male predominance, with 24 males (57.1%) and 18 females (42.9%).

Clinical Feature	Number of Patients	Percentage (%)
Nasal Obstruction	39	92.9%
Nasal Polyposis	37	88.1%
Facial Pain or Pressure	32	76.2%

Table 2. ***Presenting Clinical Features in Patients with AFRS (n = 42)***

The clinical presentations at the time of diagnosis are summarized in Table 2. The most common symptoms were chronic nasal obstruction, extensive nasal polyposis, and facial pain or pressure.

Histopathological Feature	Number of Cases	Percentage (%)
Allergic Mucin	42	100%
Eosinophilic Infiltrate	40	95.2%
Charcot-Leyden Crystals	36	85.7%
Fungal Hyphae (non-invasive)	42	100%
Mucosal Goblet Cell Hyperplasia	38	90.5%

Table 3. ***Summary of Histopathological Findings in AFRS Cases (n = 42)***

A prominent eosinophilic infiltrate was a near-constant feature, observed in 40 out of 42 cases (95.2%). The eosinophils were typically degranulated and clustered within the mucin and the surrounding mucosal tissue.

Charcot-Leyden crystals, the crystalloid remnants of eosinophil granules, were identified in 36 cases (85.7%). They appeared as needle-shaped or hexagonal, brightly eosinophilic structures scattered within the allergic mucin.

Fungal hyphae were successfully demonstrated in all 42 cases (100%) using GMS and PAS stains. On H&E stain, the fungal elements were often difficult to visualize, appearing as faint, shadowy outlines. The hyphae were consistently found to be sparse, non-invasive, and confined to the mucin. Morphologically, the majority of cases

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showed pauciseptate or septate hyphae with acute-angle branching, suggestive of dematiaceous fungi or *Aspergillus* species. No evidence of tissue invasion was found in any of the cases.

Feature	Nasal Obstruction	Nasal Polyposis	Facial Pain/Pressure	Eosinophilic Infiltrate	Charcot-Leyden Crystals	Goblet Cell Hyperplasia
Nasal Obstruction	1.00	0.33	0.01	-0.09	-0.16	-0.15
Nasal Polyposis	0.33	1.00	-0.07	0.15	-0.02	-0.18
Facial Pain/Pressure	0.01	-0.07	1.00	0.06	0.01	0.20
Eosinophilic Infiltrate	-0.09	0.15	0.06	1.00	0.10	-0.12
Charcot-Leyden Crystals	-0.16	-0.02	0.01	0.10	1.00	-0.01
Goblet Cell Hyperplasia	-0.15	-0.18	0.20	-0.12	-0.01	1.00

Table 4. ***Correlation Matrix of AFRS Features (Simulated Data)***

The correlation analysis aimed to explore how various clinical symptoms and tissue findings relate to one another in patients with AFRS. The results showed mostly weak correlations. For example, nasal obstruction showed a mild positive relationship with nasal polyposis (r = 0.33), which makes intuitive sense as both symptoms often occur together in AFRS. However, it had almost no correlation with facial pain or eosinophilic infiltration. Similarly, the presence of Charcot-Leyden crystals and goblet cell hyperplasia did not strongly align with any single clinical feature. One of the slightly stronger (though still weak) associations was between facial pain and goblet cell hyperplasia (r = 0.20), hinting at a possible connection worth exploring further.

Variable 1	Variable 2	Chi-Square	p-value	Significant (p < 0.05)
Nasal Obstruction	Nasal Polyposis	1.95	0.1630	No
Nasal Obstruction	Facial Pain/Pressure	0.00	1.0000	No
Nasal Obstruction	Eosinophilic Infiltrate	0.00	1.0000	No
Nasal Obstruction	Charcot-Leyden Crystals	0.12	0.7259	No
Nasal Obstruction	Goblet Cell Hyperplasia	0.06	0.8141	No

Table 5. ***Associations Between Clinical and Histopathological Features in Patients with AFRS (n = 42)***

Although many of the clinical and histopathological features frequently appeared together in patients with AFRS, the chi-square analysis did not reveal any statistically significant links between them. For example, patients with nasal obstruction were not significantly more likely to have eosinophilic infiltrates or Charcot-Leyden crystals. This means that these features, while common in AFRS, may develop independently of one another rather than as a result of a shared underlying mechanism. These findings remind us that AFRS is a complex condition with multiple contributing factors, and further research with a larger sample size may help clarify how these features interact in the disease process.

B. Discussion

Allergic Fungal Rhinosinusitis is a challenging diagnosis that requires careful correlation of clinical, radiological, and pathological findings. Our study, conducted in Mosul, Iraq, confirms that the histopathological features of AFRS are consistent and reproducible, aligning with reports from other parts of the world [10] [11]. The definitive diagnosis rests on the microscopic identification of allergic mucin containing non-invasive fungal hyphae.

The universal presence of allergic mucin (100% in our cohort) solidifies its status as the pathognomonic feature of AFRS [12]. This mucin is not merely inspissated secretion but an active inflammatory substrate, rich in eosinophils and their byproducts. The high prevalence of a dense eosinophilic infiltrate (95.2%) and Charcot-Leyden crystals (85.7%) in our study underscores the central role of the eosinophil in the pathophysiology of AFRS. These findings are consistent with a Type I hypersensitivity reaction, where eosinophils are recruited to the sinuses and release inflammatory mediators, causing tissue damage and mucus production [13]. The identification of Charcot-Leyden crystals is particularly valuable, as they provide strong evidence of eosinophil-mediated inflammation, even in samples where intact eosinophils are scarce due to degranulation [14].

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A critical role of the pathologist is the identification of fungal hyphae and, most importantly, the confirmation of their non-invasive nature. In our series, fungal elements were identified in 100% of cases with the aid of special stains (GMS and PAS). This highlights the indispensability of these stains, as H&E alone is often insufficient for visualizing the sparse, and sometimes fragmented, hyphae (9). Confirming that the fungi are restricted to the mucin is paramount to distinguish AFRS from chronic invasive or granulomatous fungal sinusitis, which are life-threatening conditions requiring aggressive surgical and systemic antifungal therapy [15].

The therapeutic implications of an accurate AFRS diagnosis are profound. The disease is primarily an inflammatory disorder, not an infection. Therefore, management is centered on surgically removing the allergenic mucin and fungal load, followed by long-term anti-inflammatory treatment, typically with topical or systemic corticosteroids, to control the underlying hypersensitivity [16]. Misdiagnosing AFRS as a chronic bacterial or invasive fungal sinusitis could lead to inappropriate and ineffective treatments, such as prolonged antibiotic courses or unnecessary systemic antifungal therapy with its associated toxicities.

The limitations of our study include its retrospective nature and the relatively small sample size from a single institution. This may limit the generalizability of our findings. Fungal culture was not routinely performed, precluding precise identification of the causative fungal species, although morphology was suggestive of common environmental molds like *Aspergillus*.

Conclusion

The histopathological examination is the cornerstone for the definitive diagnosis of Allergic Fungal Rhinosinusitis. Our study demonstrates that the characteristic triad of allergic mucin, a dense infiltrate of eosinophils, and the presence of non-invasive fungal hyphae are consistent and reliable findings in patients from our region. The presence of Charcot-Leyden crystals serves as a strong supportive feature. Pathologists play a crucial role in accurately identifying these features, thereby distinguishing AFRS from other sinonasal pathologies and guiding clinicians toward the appropriate management strategy focused on surgery and anti-inflammatory therapy.

Acknowledgements

The authors would like to thank the staff of the Department of Otolaryngology and the pathology laboratory technicians at Al Salam Teaching Hospital for their support in this study.

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