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Allergic Fungal Sinusitis (Presentation & Management)

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Abstract: ***Allergic fungal Rhinosinusitis (AFRS) defined as a chronic rhinosinusitis which occur in an immune competent patient with an allergy to fungus, approximately (7%) of all chronic rhino sinusitis caused by this entity. The criteria for diagnosis are still under debate as several authors have proposed their own rules. This study was conducted to clarify the age, sex, main presentation of AFRS and its methods of management. To identify the main associated factors and the role of CT- Scan in diagnosis of this disease. During nine months period from April 2009 through December. 2009 a total of (10) patients with AFRS in otolaryngology department in Medical City in Baghdad were included in this study. Every patient was assessed by thorough history and careful physical examination, plain x-ray of nose and Paranasal sinuses and CT- Scan was done for all of them. Data were collected in a questionnaire design and arranged in tables and charts for analysis. Most of patients were below the age of thirty (7=70%) with equal incidence in males (5=50%) and females (5=50%). Unilateral nasal obstruction were the most common presenting symptom (6=6%), and nasal polyps were the most common sign(8=80%), (4=40%=unilateral)&(4=40%=bilateral). Most of the patients (7=70%) had allergic rhinitis and the majority (6=60%) of them required surgical treatment. In conclusion, this study revealed that AFRS is a disease of young age with chronic course and multiple recurrences with equal incidence in males and females and need prolonged intranasal steroid therapy and surgical debridement.***

Keywords: Allergy, fungal, Rhinosinusitis

1. Allergic Fungal Rhinosinusitis

Chronic or indolent invasive fungal rhinosinusitis

This is one of the less frequent forms of fungal rhinosinusitis, most of them being reported in northern Africa and Asia. Two forms are described: granulomatous and non granulomatous, based on presence of granulomas within tissues. Most patients are immunologically competent. [1]

It is characterized by a clinical presentation where pain is the main symptom. An asymptomatic period frequently occur, symptoms appearing only when the orbit or skull base are involved. Chronic headache, proptosis and cranial nerve. [2]

Nasal endoscopy reveals nasal congestion or polypoid mucosa and sometimes a soft tissue mass covered by normal or ulcerated mucosa. Radiological appearance show opacification with bone erosion extend to the orbit and/or skull base. Histopathology reveals fungal invasion of the tissue: bone, mucous membrane, vessels. mycologic culture lead to identification of the species.

Treatment in most of the patients consists of a combination of surgery and antifungals chemotherapy. A long term clinical and radiological follow up is required to identify and treat recurrent disease. [1]

Acute fulminant fungal rhinosinusitis

This is characterized by a mycotic infiltration of the mucous membrane of the nasal cavity and/or paranasal sinuses. It occur in immunocompromised patient (AIDS, hematologic disease, type one diabetes mellitus) with a fatal outcome in the absence of treatment. The initial symptoms are often subtle, even in at risk patients. Fever or rhinorrhea are the most common first symptoms. Laterproptosis, ophthalmoplegia and focal nurological signs occur. Nasal endoscopy identify discoloration (black, necrotic turbinate), granulation, ulceration or crustsin the nose. Most frequent sites involved are middle turbinate, the septum, and rarely inferior turbinate. Mucoracae and Aspergillus are frequently isolated. [3]

Allergic fungal rhinosinusitis (AFRS)

Allergic fungal rhinosinusitis (AFRS), is defined as an immune competent patient with an allergy to fungus. Since initial publications, approximately 7% of all chronic rhino sinusitis cases requiring surgery have been diagnosed as AFRS, especially in the United States. [4] The fungi which are the cause of hyper sensitivity reside in the mucin and provide continued stimulation it is suggested that it has a similar a etiology to allergic bronchopulmonary aspergillosis (ABPA), for which several stages have been described depending on the presence of major or minor criteria for diagnosis. This pulmonary pathology concerns only Aspergillus although for AFRS, the most common fungi reported are dematiaceous species (Bipolaris, Curvuluria, Alternaria) and more rarely aspergillosis although it was originally reported in the first cases. [5]

Some countries are more commonly represented especially where the climate is warm & humid, but warm dry climates can also be associated with this pathology. Recently, a prospective study in some centers in the United States was per formed and, although the technique to identify fungal agent was not described, it appear that cases of AFRS occur more frequently in the southern central united states. In

contrast, mould count did not seem to correlate with the incidence of AFRS in this analysis. [6]

Table 1: Classification of fungal sinusitis [4]

Category and course	Immune state	Sinus involvement	Pathology	Organism	Role of fungus	Treatment
fulminant (acute)	Compromised	Single or multiple	Tissue & vascular invasion and necrosis	Aspergillus	Pathogen	Radical debridemt S, anti fungal
Chronic, irdolent	Competent non atopic	Single or multiple	Tissue invasion granuloma	Aspergillus dematiaces	Pathogen	Debridement + S.A.F
Mycetoma (chronic)	Competent non atopic	Single	Fungus ball	Aspergillus	Saprophyte	Debridement + aeration
Allergic fungal sinusitis (chronic)	Competent atopic	Multiple	Allergic mucin	Aspergillus dematiaces	Allergic	Debridement + aeration + steroids

The patho-physiology of the condition remains subject to considerable discussion as several factors are probably necessary for the development of this disease. One of the hypotheses is represented by the inhalation of u fungi which in cases of atopic patients provokes an antigenic stimulus and an inflammatory response of the mucous membrane.

The resulting edema is associated with the production of an allergic mucin, defined as a thick green to gray lamellate of dense inflammatory cells, mostly eosinophils, in various stages of degradation, Charcot-Leyden crystals and fungal hyperhae. [7]

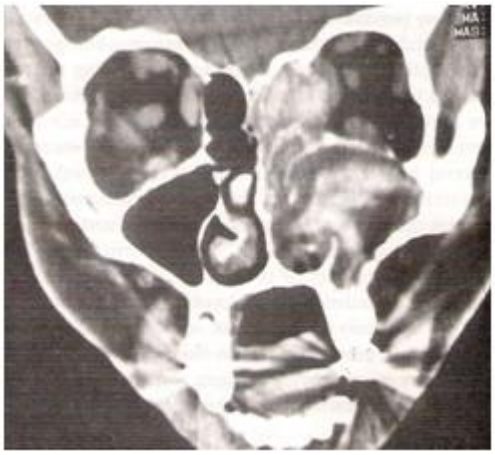


Figure 1: Unilateral allergic fungal sinusitis [2]

Nevertheless, the term allergic mucin is inappropriate according to recent studies analyzing the presence of these criteria in patients suffering from chronic rhinosinusitis with an abundant thick mucin. According to these results the term (eosinophilic mucin) with or without fungus seem to be appropriate [8]. Recently, a new hypothesis has been suggested concerning the presence and production of microbial T cell superantigens but this theory, requires further studies and analysis to be definitely accepted. [5]

The criteria for diagnosis are still under debate, as several authors have proposed their own rules. Nevertheless, the presence of allergy manifested as type 1 hyper sensitivity is increasingly essential for diagnosis. Clinically, most patients are in young age group (approximately 30 years of age), either male, or female. Bilateral, but also unilateral polyps are present in the nose associated with complete opacification of sinus cavities on CT scan associated frequently with bone expansion, although expanding inflammatory lesion are common and highly suggestive of fungus, no direct invasion of dura or periorbita is seen. [9]

The presence of hyphae in the mucin associated with eosinophils is one of the major criteria for the diagnosis. Culture is necessary to identify the actual fungal agent but no growth is frequently observed. Type 1 hyper sensitivity test (RAST) or (skin test) appears to be minimal allergy test to perform for the diagnosis. [7]

Other investigations, such as total eosinophil count, total serum lg E, antigen specific lg E or lg G (if available), are suggested to reinforce the diagnosis. Ig E levels are frequently higher than in the normal population. Allergic rhinitis, which studied, is generally more frequently found in cases of AFRS. [10]

Treatment

Treatment is controversial. Even though the removal of all the mucin is recommended by almost all authors, recurrences are quite common which leads to combination with medical therapy, an area still under debate. An endoscopic mucosal staging system has been suggested to evaluate the post operative management. Prednisilone is the oral steroid most commonly given in this period. [11]

Nevertheless, length & dosage are not clearly defined. Simultaneously, topical intranasal steroid is prescribed for at least one year. [12]

Topical & systemic antifungal therapy is not actually considered as sufficiently efficacious in this condition. Immunotherapy was studied by Mabry et al. with a small group of patients in a non randomized study. In this protocol immunotherapy was started after complete removal of the allergic mucin and conservation of the underlying mucosa. Fungal antigens and positive non fungal antigens were injected weekly during the first year up to a maximum tolerated dose. Although no data are available about the length of treatment, injections were continued for at least 3 years with an increased interval between treatment (two to three wks). With this treatment the author observed that immunotherapy reduces the necessity for systemic and nasal corticosteroid and it also limit recurrences. To confirm these results in a limited number of patients, multicentre study is ongoing. [8]

Nevertheless, some problems remain and this therapy is totally in effective in some individuals. This approach is promising but is limited by the lack of availability of all

fungal antigens and the necessity for accurate identification with culture in all clinical cases. [8]

Patients & Methods

A prospective study of 10 patients with allergic fungal rhinosinusitis were done in the department of otolaryngology in the hospital of surgical specialization/ medical city / Baghdad

All were subjected to thorough history, examination and investigations which included plain sinus X-ray and CT scan of paranasal sinuses these were included in a questionnaire design which included the patient age, sex, occupation, residence, & chief, complain and duration, past medical & surgical history, social, family history and history of drug allergy. Then examination of the nose, throat, ear & neck were obtained in addition to general examination. The radiological investigations included the plain sinus x-ray (waters view) and CT scan of nose & paranasal sinuses

Medical treatment by topical nasal steroid & systemic steroid were prescribed for them with oral antifungal drugs before and after surgical treatment.

Some of them were admitted for surgical debridement which included conventional surgical removal of polyps and functional endoscopic sinus surgery. The material removed during surgery were sent for histopathological and fungal study.

2. Questionnaire

Patient no. sex: age: occupation:
Residence: (rural; urban) date:
History: nasal obstruction: bilateral; unilateral (duration)
Nasal discharge (anterior; posterior); facial pain; epistaxis; loss of smell (partial, complete); sneezing.
Past medical hx: bronchial asthma; allegic rhinitis
Past surgical hx:
Family hx:asthma ;others
Social hx:smoking;drinking
Drug hx:allergy to pencillin;asprin
Examinaton: nasal exam:
polyp(unilateral;bilateral): endoscopic exam:
Throat exam:post nasal drip
Ear exam:
Investigations: plain x-ray (watrs); CT scan (coronal)
Treatment:medical/systemic steroids Local steroid
Antifungal
Surgical/FESS; conventional
Biopsy result/histopathological study; fungal stain

3. Results

1. In this study of 10 patients AFRS the gender of patients was equal 5 males (50%) and 5 (50%) was females.

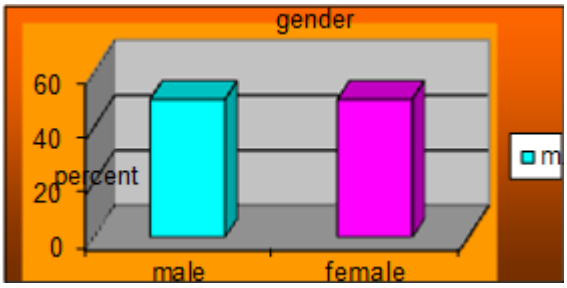


Table 2: Gender

	Number	%
Males	5	50
Females	5	50
Total	10	100

2. The age of patients range from 6-57 years 2 patients (20%) less than 10Yr. 3 patient (30%) between 10-19 Yr., 2 (20%) between 20-29 Yr. & 1 pt between 30-39 & 2 (20%) more than 40 Yr. so peak incidence is in age group between 10-19 Yr.

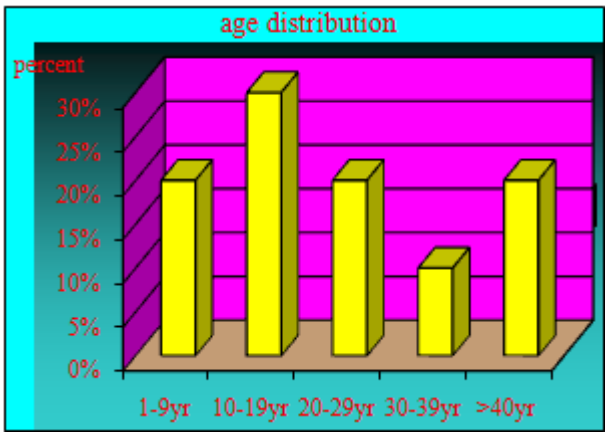


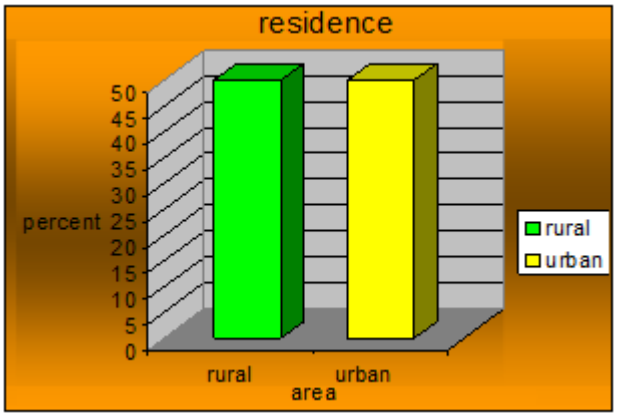
Table 3: Age distribution

Age	Number	%
1-9	2	20
10-19	3	30
20-29	2	20
30-39	1	10
≥ 40	2	20
Total	10	100

3. Residence of patient in this study was equal in both rural & urban areas 5 (50%) in rural & 5 (50%) in urban.

Table 4: Residence

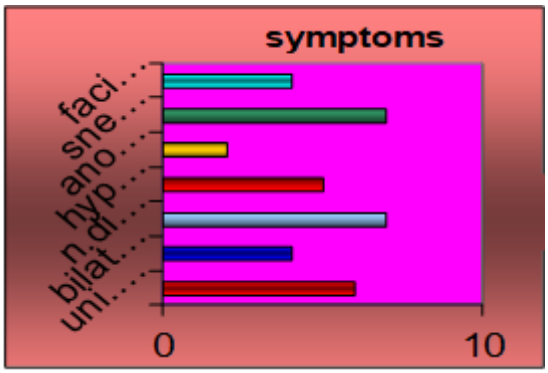
Residence	Number	%
Rural	5	50
Urban	5	50
Total	10	100

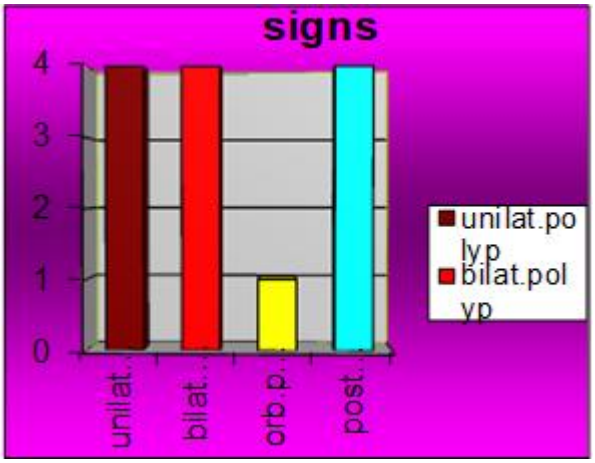


4. Presentations of AFRS: unilateral nasal obstruction was (6=60%) more than bilateral nasal obstruction (4=40%), nasal discharge was anterior in (7=70%) & posterior drip in (4=40%). Rt. nasal (5=50%), Lt. (1=10%) facial pain in (4=40%), loss of smell was complete in 2(20%) & partial in (5=50%) & Sneezing present in 7(70%) of pt., Epistaxis not present in any case. Unilateral nasal polyp was present in (4=40%)) pt. & bilateral nasal polyp in (4=40%) pt. & no polyp was found in (2)=20%.

Table 5: Signs & symptoms

S&S	Number	%
Uni-nasal obstruction	6	60
Bilateral nasal obstruction	4	40
Nasal discharge	7	70
Partial loss of smell	5	50
anosmia	2	20
Sneezing	7	70
Facial pain	4	40
Unilateral polyp	4	40
Bilateral polyp	4	40
Orbital proptosis	1	10
Previous polypectomy	5	50
Previous surgery	2	20
Post nasal drip	4	40
Epistaxis	0	-

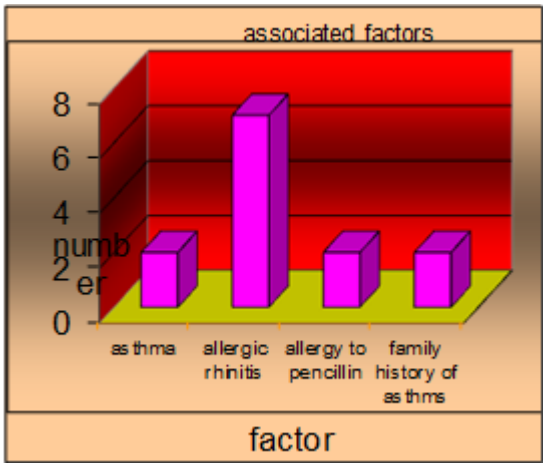




5. Association with other factors: From these 10 pt. 2(20%) were having bronchial asthma & 3(30%) had family hx of asthma, 3 (30%) was smoker's, 2(20%) had allergy to penicillin & allergic rhinintis were founded in 7 (70%) patients.

Table 6: Associated other factors

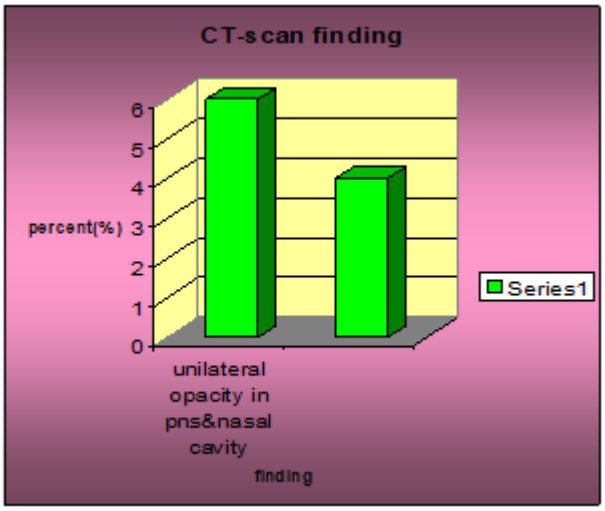
Factor	Number	%
Bronchial asthma	2	20
Allergic rhinitis	7	70
Family hx of asthma.	2	20
Allergy to penicihin	2	20
Allergy to asprin	-	
Smoking	3	30

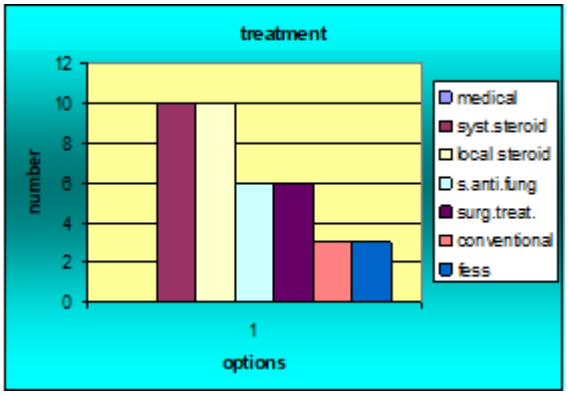


6. The main investigations done for them were plain X-Ray of nose & Paranasal sinuses (Water's) view (10=100%) and CT scan for (10=100%) patients. In CT scan bilateral hetrogenerous opacity with variable calcification in the Paranasal sinuses were founded in (4=40%) while unilateral involvement of sinuses & nasal cavity were (6=60%).

Table 7: CT scan finding

Finding	Number
Unilateral soft tissue mass in maxillary, ethmoid, sphenoid & nasal cavity.+bone erosion	6
Bilateral soft tissue-mass in ParaNasalSinuses & nasal cavity with bone erosion & scattered calcification	4
Total	10





7. **Treatment**: medical treatment by systemic & local steroid in (10=100%) and systemic antifungal in (6=60%) of them. Surgical treatment was offered to (6=60%) pt. From those who underwent surgery 3 (30%) treated by functional endosopic sinus surgery (FESS) and 3 (30%) treated by conventional polypectomy and aereation of sinuses. One patient of them treated by caldwell-luc operation to clear the maxillary antrum.

Table 8: Treatment

Medical Rx	
Local steroid	10
Systemic steroid	10
Systemic antifungal	6
Surgical Rx	6
Conventional surgery	3
FESS	3

8. **Histopathological** study for the specimen taken by surgery was found to be positive for allergic fungal rhino sinusitis in 4 (40%)

4. Discussion

Gender in our study there is equal sex distribution of AFS in both males and females patients (5 male : 5 female). Torres et al studied 16 cases of AFS and showed male predominance (10 males and 6 females), while Sohail et al in study of 32 cases recorded female predominance (11 males and 21 fmales) Courley et al reviewed 200 consecutive cases of chromic sinusitis requiring surgery and found 14 cases (7%) of AFS with equal frequency in males & females. [2]

Table 9: Clinical, radiological, and fungal culture results ofAFRS for 10 patients.(summary)

Case No.	Age (Yr.)	Sex	Clinical presentation	hx of atopy (clinical dx)	CT scan finding	Recurrence	Culture
1	24	Male	1Yr. of bilateral nasal obstruction & discharge	Hx of allergic Rhinitis	Soft tissue masses with multiple & bilateral sinuses+ bone erosion	No	
2	7	Male	1Yr. of bilateral nasal obstr. & discharge & extensive polyposis filling nasal cavities	Hx of allergic Rhinitis +asthma	Soft tissue mass involve multiple & bilateral sinus + bone erosion	Recur (one) polypectomy (LA)	N/A
3	36	Male	2Yr. of bilateral nasal obstr. & discharge with extensive nasal polyps	Allergy to penicillin no atopy	Hetetrogenous opacities fill the whole sinuses with calcification	Recur (2) polypectomy	N/A
4	10	Female	3 Mo. unilateral nasal obstr. & discharge it nasal polyp	Allergic.rhinitis+Asthma	Lt. soft tissue mass involving whole Lt. sinuses	No	N/A
5	57	Female	10 Mo. Unilateral nasal obstr. (Rt)	No	Rt. Sphenoid opacity with calcification	No	N/A
6	40	Male	6 Mo. Unilateral nasal obstr. & discharge (Rt) nasal polyp.	Allergic rhinitis	Rt. Pan sinuses involved by hetrogenous soft tissue mass + bone erosion	Recur (one)	+ve
7	6	Female	6 Mo. Unilateral nasal obstr. & discharge + Rt. Orbital swelling Rt. nasal polyp.	Allergic rhinitis	Rt. Soft tissue mass maxillary, ethmoid, frontal & sphenoid + bone erosion.	Recur (one)	+ve
8	12	Female	6 Mo. Bilateral nasal obstr. And discharge, extensive nasal polyp reach anterior nares+ telecanthus+proptosis	Allergic rhinitis	Soft tissue mass involving both sides of sinuses	Recur (2)	+ve
9	18	Female	6 Mo. Unilateral (Rt) No. pervious Rt. Polypectomy	No	Rt. Maxillary ethm soft tissue mass with bone erosion	Recur (one)	N/A
10	28	Male	1 Yr. unilateral (Rt) nasal obtr. & discharge Rt nasal polyp pervious polypectomy.	Allergic rhinitis	Rt. Maxillary, ethm. Frontal sphenoid soft tissue mass + bone erosion.	Recur (one)	+ve

Age
In this study age range from 6-57 Yr. and most of the patients are in the second decade of their life (3= 30%) and about 70% are below the age of thirty. In Torres et al study (11 patient of 16= 68, 75%) were under the age of thirty. [2] Sohail et al noticed 21 of 32 patients (65%) were below the age of thirty, it is a disease of young age. [3]

Symptoms and signs
In this study of 10 patients the main presenting symptom was nasal obstruction (100%) both unilateral obstruction which predominate (6=60%) and bilateral nasal obstruction (4=40%) followed by rhino rhea (7=70%) and post nasal drip with facial pain, hyposmia in less number. very high number (7=70%) had multiple recurrences and previous polypectomy. Most frequent sign was nasal polyp which present in (8=80%) with unilateral involvement in 4=40% and bilateral in (4=40%).

Earlier, AFS was considered to be an essentially unilateral disease. Bent and Kuhn have described "unilateral predominence" in AFS on the other hand [6], Marple found 51% bilateral disease in 45 cases. [13] Torres et al showed the same observation that the most frequent symptom was nasal obstruction and discharge which occurred in all cases (16)= 100% but he noticed bilateral involvement more frequent (9) and unilateral in 7 (44%). [2]

Sohail et al revealed the same symptom of nasal obstruction with prolonged period of at least 6 mouths but with unilateral predominance (22 of 32)(69%) [3] and this agree with our study he also noticed the multiple recurrences which occur in 8 of 32 patients after treatment with medical and surgical (25%). Torres et al also found recurrence in 4 cases at 8, 11, 12 & 18 months after the initial surgical procedure. [2]

Associated factors: In our study 7 (70%) had allergic rhinitis and 2 (20%) had bronchial asthma and 2 (20%) had family Hx of asthma. In Torres et al study 6 patients a history of atopy manifested as allergic rhinitis (3), asthma (1), wheezing (1). Sohail et al showed that most of their patients have elevated lg E levels especially those with recurrence. All the patients was immune competent in our study (10) and didnot have diabetes and this was also noticed by Sohail et al & Torres et al. [2, 3]

The main investigation done in our study was plain X-Ray of the nose and PNS (water's) view (10) and CT scan of nose & PNS (coronal) view. The main finding in CT scan was unilateral soft tissue mass involving nasal cavity, maxillary, ethmoid, sphenoid & frontal sinuses in variable degrees with variable calcification (6=60%) & bilateral involvement of both sinuses was found in (4=40%) this was associated with variable degree of bone erosion. Torres et al mentioned that radiological studies using CT scan and MRI showed soft tissue masses occupying the nasal cavity or multiple PNS in all cases. In 12 of 16 cases, bone erosion, including three cases with destruction of the clivus was reported. Sinus involvement was unilateral in 7 of 16 and bilateral in the remainder (9). CT scan is an important tool for diagnosis; it is one of the diagnostic criteria of AFS by the characteristic finding of heterogeneous opacity with bone erosion but without destruction. Also it is important in staging of the disease and showing its extent there by determine the need for surgical procedure and the type of procedure performed. Sohail et al used the CT scan also in the fellow up of patients underwent surgical procedures to detect the recurrence of the disease and response to medical treatment. [2, 3, 9]

Treatment
Medical treatment in the form of local nasal steroid and systemic steroid mainly predniselone in tapering dose for prolonged period for at least 1 month and this was offered for 10 cases but antifungal in the form of ketoconazole tablet offered for (6) patients both pre and post operatively. Sohail et al stated that corticosteroids, antifungal mediations and immune therapy have been used as post operative medical therapy. [13] Therapy has shown promising results, corticosteroids are still the most commonly used post operative medical therapy. [14] Most of anthers prefer systemic steroid to nasal steroid spray. Kinsella et al found a very high rate of recurrences when nasal steroid spray was used as the sole post operative therapy. [15] In Sohail et al study 32 cases 15 of them received nasal steroid only and 17 received systemic steroid as post operative medication. [3] The incidence of recurrence was 4 in both groups. Torres et al stated that current impacted mucin and aeration of diseased sinuses. [2] Systemic steroid have been used successfully in cases of recurrence AFS, but their potential side effects limit their use. Topical intranasal steroids and saline irrigation have been safer, but their benefit nose not been proven in cases of AFS. Systemic antifungal agents are of no effect in non invasive fungal sinusitis. [9] However topical antifungal irrigation solution may play a role in eliminating residual fungal antigens, although no data are available regarding the efficiency of its clinical use. [16] Recurrences, sometimes multiple are common in AFS, although no prospective study of long term results have been performed 5 of 8 of Torres patients with at least 6 months of fellow up developed one or more recurrences from 8 months to 4 years after initial surgical procedures. In our study of 10 cases 6 underwent surgical procedure to treat AFS (3) was by FESS with removal of polypoidal tissue and allergic mucin with aeration of maxillary sinuses the other 3 patients had conventional surgical procedure in the form of polypectomy and antrostomy and 1 case underwent cald well-luc procedure to clear the maxillary sinus. Sohail et al mentioned that surgery play an important role in the treatment of AFS. This should include opening and, if necessary, widening of ostium of involved sinuses and complete removal of inciting fungal mucin. [17] It should achieve un obstructed long term postoperative drainage and ventilation of involved sinuses Bradly et al feel that inadequate initial surgery was an important contributory factor to recurrence in their cases. [18]

Histopathological study and fungal study: In this study from 6 patients underwent surgical therapy for AFS 4 of them had positive result for AFS and 2 of them the result was unavailable. Torres et al showed the histological features of all specimens were similar. It consists of fragments of edematous respiratory mucosa containing a mixture of acute and chromic inflammatory cell infiltrate. [10] Abundant basophilic mucin with laminated appearance

that consisted of densely packed bands of mixed inflammatory cell infiltrate, predominantly eosinophils, necrotic debris, sloughed respiratory epithelial cells, and Charcot-leyden crystals, alternating with less cellular mucinous material was noted near the mucosa. [19] Scattered fungal hyphae within the mucin were identified in all cases. They were identified by GMS stained sections in all cases and were observed orn Fontana-Masson stains in all but one case. However, the Fontana-Masson stain showed a clearer background and identified the fungal organisms better and more easily than GMS stain. The fungal hyphea showed dichomoter branching at 45-degree angles and had moderately irregular contours. [20]

5. Conclusion and Recommendation

Allergic fungal sinusitis is a disease of young age which occurs equally in both sexes and associated with atopy in most of patients. It needs a prolonged steroid therapy as main treatment option in addition to good surgical debridement. AFS associated with multiple recurrences even after prolonged medical and surgical therapy, it is a difficult disease to diagnose and difficult to treat with unpredictable prognosis and cure.

We recommend many other researches to be done in this subject to enhance both diagnostic ability of the physician about this disease and the ability to treat it without recurrence or at least a few recurrences.

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