FUNGAL RHINOSINUSITIS

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Abstract: Fungi are a major part of the ecosystem. In fact, over 250 fungal species have been reported to produce human infections. More than ever, fungal diseases have emerged as major challenges for physicians and clinical microbiologists. The aim of this study was to summarize the diagnostic procedures and endoscopic surgical treatment of patients with fungal rhinosinusitis.

Eleven patients, i.e. 10\% of all cases with chronic inflammation of paranasal sinuses, were diagnosed with fungal rhinosinusitis. Ten of them were patients with a noninvasive form, fungus ball, while only one patient was classified in the group of chronic invasive fungal rhinosinusitis which was accompanied with diabetes mellitus. All patients underwent nasal endoscopic examination, skin allergy test and had preoperative computed tomography (CT) scans of the sinuses in axial and coronal plane. Functional endoscopic sinus surgery was performed in 10 patients with fungus ball, while a combined approach, endoscopic and external, was done in the immunocompromised patient with the chronic invasive form of fungal rhinosinusitis.

Most cases (9/11) had unilateral infection. In 9 cases infection was restricted to a single sinus, and here the maxillary sinus was most commonly affected (8/9) with infections in other patients being restricted to the sphenoid sinus (1/9). Two patients had infections affecting two or more sinuses. In patients with an invasive form of the fungal disease there was involvement of the periorbital and orbital tissues. In patients with fungus ball the mycelia masses were completely removed from the sinus cavities. Long-term outcome was positive in all the operated patients and no recurrence was detected. The most frequent fungal agent that caused rhinosinusitis was Aspergillus. Mucor was identified in the patient with the invasive form.

Endoscopic examination of the nasal cavity and CT scanning of paranasal sinuses followed by endoscopic sinus surgery were represented as valuable diagnostic and therapeutic procedures for fungal rhinosinusitis.

Key words: fungal rhinosinusitis, endoscopic evaluation, CT scanning.
Introduction

Fungi are a major part of the ecosystem. In fact, over 250 fungal species have been reported to produce human infections. More than ever, fungal diseases have emerged as major challenges for physicians, clinical microbiologists and basic scientists. From the common Candida infections to the deadly aspergillosis, fungal infections influence all levels of clinical practice.

Over the last two decades, it has become clear that it is important to classify fungal rhinosinusitis to accurately predict prognosis and optimize effective therapy. This classification is founded on the immunological relationship of the fungus to the host [1]. There are two basic types of fungal disease: invasive and noninvasive. These may be further subdivided into five distinct entities according to the patient’s immunological status.

Acute invasive rhinosinusitis occurs only in immunocompromised patients and the greater the source of the immunocompromise, the more fulminating the course. Some have termed this entity acute or fulminant invasive fungal sinusitis. The term fulminant conveys the rapidly destructive and often fatal nature of this disease entity, which occurs if the patient’s invasive fungal disease is untreated or if the patient’s immunocompromise is severe and irreversible [2].

Chronic invasive form may occur in mildly immunocompromised patients or in patients who appear immunocompetent. DeShazo et al. subsequently divided chronic invasive fungal rhinosinusitis into two subtypes according to histopathology: granulomatous invasive fungal rhinosinusitis and nongranulomatous form, but no difference in prognosis or therapy is yet apparent based on this distinction [2].

Fungus balls, occasionally referred to as mycetoma [3], consist of tangled mats of hyphae present in the sinuses. Paranasal sinus fungus balls show no evidence of invasion on histopathology [4]. Immunocompetent patients with fungus balls are best treated with surgical removal of the fungus ball.

Saprophytic fungal colonization is defined as a visible growth of fungus within the nasal cavity of an asymptomatic individual and does not refer to fungi that are not visibly growing but present by culture alone. Saprophytic fungus infestation refers to the presence of fungal spores on mucous crusts within the nose and paranasal sinuses and as fungus balls occur in immunocompetent individuals.

Allergic fungal rhinosinusitis is defined as patients with an allergy to the fungus who demonstrate an allergic mucinous response to the fungi containing numerous eosinophils and Charcot-Leyden crystals. In a sense, it is the other end of the immunological spectrum, i.e. patients are too immunocompetent.
All these aforementioned clinical manifestations may overlap or progress from a noninvasive form into an invasive form of fungal rhinosinusitis if the immunological status of the patient changes.

We have encountered this specific form of chronic rhinosinusitis over the last seven years and this experience has allowed us to formulate the aim of this study, that is to summarize the diagnostic procedures and endoscopic surgical treatment of patients with fungal rhinosinusitis.

**Material and methods**

One hundred and ten patients were diagnosed with chronic rhinosinusitis and underwent nasal endoscopic sinus surgery at the University ENT Clinic, Skopje, Macedonia from January 2006 to December 2011. Among these 11 cases, i.e. 10%, were diagnosed with fungal rhinosinusitis. Ten of them were patients who had a noninvasive form, a fungus ball, while only one patient was classified in the group of chronic invasive fungal rhinosinusitis (CIFR) which was accompanied by diabetes mellitus.

The study included 4 male and 7 female patients with fungal rhinosinusitis. The average age was 41 years (range: 24 to 69 years) and the average duration of symptoms was 15 weeks (range, 4 weeks to 2 years).

Preoperative management included completion of a sinusitis-related symptoms questionnaire and thorough rhinologic history. All patients underwent a nasal endoscopic examination and skin allergy test, immediate or delayed, before operation.

All cases had preoperative computed tomography (CT) scans of the sinuses in the axial and coronal planes and were diagnosed for fungal rhinosinusitis according to the following criteria: (1) symptom duration of at least 4 weeks; (2) CT scan showing opacification and mucosal thickening in one sinus or unilateral nasal cavity, presence of focal or diffuse areas of increased attenuation in the sinus due to the deposition of ferro-magnetic elements in the fungal masses, and bone erosion or expansion; (3) microscopic examination of fresh clinical specimens with Lactofenol blue and/or histopathological preparations of the sinus mucosa stained with haematoxylin/eosin (H&E), showing the presence of fungal hypha within the sinus mucosa.

General anaesthesia was administered with additional intranasal topical application of Oximetazolini hydrochloridum 0.5 mg/ml. Functional endoscopic sinus surgery was performed in 10 patients with a fungus ball, while a combined approach, endoscopic and external was done in the immunocompromised patient with CIFR. The extent of the surgery was determined by the extent of the disease and included, infundibulotomy with middle meatal antrostomy,
performed in all 11 patients, anterior ethmoidectomy and perforation of the
ground lamella of the middle turbinate with posterior ethmoidectomy in 2 pa-
ients and sphenoidotomy in only one case. Anatomic landmarks including the
lamina papiracea, periorbit, and the skull base were used to estimate the safety
margins of the surgery. Only the patient with CIFR underwent surgical debride-
ment using the combined approach, endoscopic and external. Postoperatively
the patient was treated by injection of 1 g of amphotericin B for 15 days and
then oral itraconazole, 0.2 g daily for 14 days. In the patients with a fungus ball
antifungal therapy was not administered after the surgery. The total number of
surgical procedures is higher than the number of patients due to multiple proce-
dures performed in one patient.

All patients were reviewed regularly following surgery to perform
endoscopic cleaning of crusts and mucus. After discharge from hospital, out-
patient visits were performed until the postoperative wound healing was
completed. Follow-up periods for all patients were more than six months.

Nasal discharges, sinus aspirates and pathological tissues in the sinus
were collected for fungal smear (Lactofenol blue) and cultivation (Sabouraud’s
agar) during and immediately after the operation. Mucosa from the infected
sinus was separately stained with Haematoxylin/eosin (H&E).

**Results**

Clinical manifestations were unilateral purulent nasal discharge (8 pa-
ients), nasal obstruction (7 patients), headache (4 patients), a peculiar smell in the
nose (3 patients) (Table 1).

During nasal endoscopy there was a bloody discharge in the middle
meatus in 2 while purulent nasal secretion was detected in 7 cases. Five patients
had an inward expansion of the lateral nasal wall. A dark brown to black coloured
part of the mycelia mass was present in the middle nasal meatus in 2 patients.

Allergy skin tests, immediate or delayed, were negative in all 11 patients.

Sinus infections were localized by CT imaging. In patients with an
invasive form of fungal infection MRI was performed. Most cases (9/11) had
unilateral infection. In 9 cases infection was restricted to a single sinus, and here
the maxillary sinus was most commonly affected (8/9) with infections in other
patients being restricted to the sphenoid sinus (1/9). Two patients had infections
affecting two or more sinuses. In patients with an invasive form of the fungal
disease there was involvement of the periorbital and orbital tissues. (Figure 1).
No case was found in which fungal pathological changes were restricted to the
frontal sinus (Table 1).
Table 1

**Clinical features, treatment, and outcome of fungal rhinosinusitis patients**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Symptoms</th>
<th>Affected sinuses</th>
<th>Therapy</th>
<th>Final Outcome</th>
</tr>
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<tr>
<td>1</td>
<td>H, NO</td>
<td>MS</td>
<td>S</td>
<td>C</td>
</tr>
<tr>
<td>2</td>
<td>PS, NO, ND</td>
<td>MS, ES</td>
<td>S</td>
<td>C</td>
</tr>
<tr>
<td>3</td>
<td>ND</td>
<td>MS</td>
<td>S</td>
<td>C</td>
</tr>
<tr>
<td>4</td>
<td>PS, ND</td>
<td>MS</td>
<td>S</td>
<td>C</td>
</tr>
<tr>
<td>5</td>
<td>H, NO, ND</td>
<td>MS, ES</td>
<td>S, AFD</td>
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<td>S</td>
<td>C</td>
</tr>
<tr>
<td>7</td>
<td>H, NO, ND</td>
<td>SS</td>
<td>S</td>
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<tr>
<td>11</td>
<td>PS, ND</td>
<td>MS</td>
<td>S</td>
<td>C</td>
</tr>
</tbody>
</table>

H = headache; NO = nasal obstruction; ND = nasal discharge; PS = peculiar secretion; MS = maxillary sinus; ES = ethmoid sinus; SS = sphenoid sinus; S = surgery; AFD = antifungal drug treatment; C = cured;

*Figure 1 – MRI – Fungal infection invading the periorbital and orbital tissues*

In patients with a fungus ball the mycelia masses were completely removed from the sinus cavities. No involvement of the sinus mucosa was detected. (Figures 2, 3). In patients with CIFR all visible disease was removed and exenteration of the right orbit was realized because of the involvement of the periorbital and orbital tissues. The right eye was amaurotic before surgery. the long-term outcome was positive in all operated patients and no recurrence was detected. There were no operative complications.
Figure 2 – CT of paranasal sinuses (coronal view) – Fungus ball in right maxillary sinus (preoperatively)

Figure 3 – CT of paranasal sinuses (coronal view) – Normal finding (postoperatively)
In all cases microscopic examination of fresh clinical specimens revealed fungal hyphae within the sinus cavities and within the sinus mucosa in patients with an invasive form. Subsequent fungal cultivation reported Aspergillus in 10 cases (Figure 4), and Mucor in one patient, the invasive form. Granulomas were absent in all cases.

Figure 4 – Aspergillus

Discussion

It is important to differentiate sinonasal fungus balls from non-fungal rhinosinusitis and other forms of fungal rhinosinusitis in order to determine optimal treatment and prognosis of the disease. In particular, a sinonasal fungus ball, a non-invasive form of fungal sinusitis, can be characterized and recognized by radiological findings before surgery.

In our study the condition of the sinonasal and neighbouring regions preoperatively were evaluated radiologically with non-contrast CT in all patients. Calcifications were found in 6 of 11 (54.5%) cases, while in the other five patients increased attenuation was not detected.

Sinus CT scan can assist diagnosis when there is bone erosion or soft tissue expansion into the orbit or the intracranial vault [5, 6].
Seo Yj et al. realized a radiological study and analysis of 119 cases with a fungus ball. Patient condition was evaluated using contrast-enhanced CT (99 patients), non-contrast CT (18 patients) and/or MRI (17 patients) prior to sinus-external surgery. The results show that calcifications were found in 67.2% of patient who underwent a non-contrast CT scan. In comparison with results from our study this is a higher percentage. As opposed to non-contrast CT scans, contrast CT scans revealed a hyper-attenuating fungal ball in 82.8% and enhanced inflamed mucosa in 65.5% of the patients, respectively. On MRI, most sinusonal fungus balls showed iso- or hypointensity on T1-weighted images and marked hypointensity on T2-weighted images. Inflamed mucosal membranes were noted and appeared as hypointense on T1-weighted images (64.7%) and hyperintense on T2-weighted images (88.2%). The results of this radiological study emphasize the value of a contrast-enhanced CT scan or MRI, because these two methods provide sufficient information for the preoperative differentiation of a sinonasal fungus ball from other forms of rhinosinusitis [7].

Recent reviews of the treatment of fungal rhinosinusitis stress the importance of carefully determining whether the disease is non-invasive, invasive or allergic. The etiological agent and the underlying immunological condition of the host also influence the choice of treatment. The various approaches to managing fungal rhinosinusitis include endoscopic surgery, topical and systemic antifungal antibiotics, corticosteroids and immunotherapy [8–10].

The treatment of a paranasal sinus fungus ball is surgical removal. In asymptomatic patients with opacification of a sinus, diagnosis of the opacified sinus results in surgical intervention and removal of the fungus ball. Should an asymptomatic patient undergo surgery for an opacified sinus without evidence of bony erosion? This is controversial, and following the patient for symptoms and repeated imaging to assess for progression is also a reasonable path. If the patient is asthmatic, then presumed persistent sinusitis may be a driving force for the asthma and surgery could be advocated.

A symptomatic patient should undergo surgery. In the past these patients were approached externally with Caldwell-Luck procedures [11], but in the last more than ten years removal of the fungus ball via functional endoscopic sinus surgery is usually performed.

The study of Ledderose GJ et al. that included forty patients diagnosed with a fungus ball, showed that functional endoscopic sinus surgery is the treatment of choice and is associated with exceptionally high patient satisfaction [12].

CIFR is a newly recognized disease and cases reported in the literature have generally been treated by surgery followed by antifungal drug therapy [13, 14].
The only immunocompromised CIFR patient in our study after six months follow-up shows no signs of local recurrence. Gumaa reported on 22 cases treated surgically and in most the outcome was favourable [15]. In the study of Yongqi L. et al, the majority of patients with CIFR treated with nasal endoscopic sinus debridement surgery had a positive outcome [16].

The most frequent fungal agent that causes rhinosinusitis is Aspergillus and that finding corresponds to the results of our study. Then follow Mucor, Candida etc. [16, 17]. Ponicau JU, et al. isolated fungi in 100% of healthy volunteers and in 96% of patients with chronic rhinosinusitis [17]. The technique employed by these investigators for obtaining cultures differs from the direct cultures or cultures of mucin reported by others and involves a wash of the nasal cavity. The specificity of fungal cultures in identifying evidence of allergic fungal rhinosinusitis or invasive fungal rhinosinusitis, using the technique of Ponicau et al, is essentially zero, because all normals also demonstrate evidence of fungal growth on culture of nasal washings.

**Conclusion**

Endoscopic examination of the nasal cavity and CT scanning of the paranasal sinuses followed by endoscopic sinus surgery were represented as valuable diagnostic and therapeutic procedures for fungal rhinosinusitis, i.e. fungus balls. Microscopic examination of specimens is the most definite and rapid method of establishing a diagnosis of fungal rhinosinusitis. Aspergillus is the common fungal agent associated witha fungus ball.

**REFERENCES**


Резиме

ФУНГАЛЕН РИНОСИНУЗИТИС

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Фунгите претставуваат голем дел од екосистемот. Повеќе од 250 фунгалини видови предизвикуваат инфекции кај луѓето. Фунгалините заболевања станаа главен предизвик за лекарите и клиничките микробиолози. Целта на студијата беше да се сумираат дијагностичките постапки и ендоскопскиот хируршки третман кај паациентите со фунгален риносинузитис.

Единаеесет паациенти, односно 10% од сите паациенти со хронично воспаление на параназалните синуси без дијагностичирани како фунгален риноси-
Фунгален риносинузитис. Каж десет пациенти беше присутна неинвазивна форма односно фунгална топка, додека само каде еден пациент со дијабетес мелитус постоеше хронична инвазивна форма на фунгален риносинузитис. Каж сите пациенти беше реализиран ендоскопски преглед на носната празнина, кожни алерготестови и беше направен предоперативен КТ скен на параназални синуси во аксијална и коронална проекција. Функционална ендоскопска хирургија на параназалните синуси беше реализирана каде 10 пациенти со неинвазивна форма додека комбинирани, ендоскопски и надворешен пристап беше направен каде пациентот со хронична инвазивна форма на фунгален риносинузитис.

Каж најголемиот број пациенти (9/11) постоеше еднострана инфекција. Каж 9 испитани беше зафатен само еден синус, и тоа најчесто максиларниот (8/9) додека каде еден пациент инфекцијата беше локализирана само на сфеноидалниот синус. Каж двајца пациенти инфекцијата беше двострана односно без афектирања два и/или повеќе синуси. Каж пациентот со инвазивна форма на фунгален риносинузитис постоеше прорак на инфекцијата во периорбиталните и орбиталните ткани. Каж пациентите со фунгална топка мицелиумските маси беше комплетно отстранети од синусните празнини. Не беше детектiran редиција на инфекција како ниту еден пациент. Aspergillus беше најчест изолиран фунгален агенс, додека Mucor беше детектиран како пациентот со инвазивна форма на риносинузитис.

Ендоскопскиот преглед на носната празнина и компјутеризираната томографија на параназалните синуси, проследени со ендоскопски хирургички третман претставуваат драгоцен дијагностички и терапевтички процедури каде фунгалниот риносинузитис.

Ключни зборови: фунгален риносинузитис, ендоскопска евалуација, компјутерска томографија.

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