ORIGINAL CONTRIBUTION

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How to diagnose sinus fungus balls in the paranasal sinus? An analysis of an institution's cases from January 1999 to December 2006

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SUMMARY

Background: *The diagnosis of a sinus fungus ball (SFB) is often not clear despite well-defined diagnostic criteria.*

Objective*: To study the radiological, intraoperative and histological diagnostic accuracy in comparison to results from mycological and histological analysis.*

Methods: *Systematic review of 724 files from patients treated for chronic rhinosinusitis from 1999 – 2006 at our institution.*

Results: *The sensitivity, specificity, positive and negative predictive value (PPV, NPV) of preoperative CT imaging was 83%, 94%, 56% and 98% respectively, whereas, based on intra-operative findings, it was 98%, 93%, 57% and 100%.*

Conclusions: *A high number of misdiagnoses was found possibly due to sampling error. A severe inflammatory reaction of the surrounding tissue was found more often in SFB than in controls in our study and this we suggest could be an additional sign for fungal infection. Fungal cultures did not contribute to a correct diagnosis.*

Key words: sinus fungus ball, diagnostic accuracy, clinical characteristics, sensitivity, specificity, histology, mycology

INTRODUCTION

Rhinosinusitis is a common disorder, estimated to affect 14% of the adult population at some time in their lives in the United States of America [(1)]. Patients with chronic rhinosinusitis suffer from long-term nasal congestion, thick nasal discharge, loss of sense of smell, fullness and headaches. Although rhinosinusitis may be due to many conditions, a distinct cause is fungal infection. About 10% of patients undergoing surgery to the nose and the paranasal sinuses have fungal rhinosinusitis [(2)]. Five basic diagnostic categories of fungal paranasal sinus disorders are currently recognized [(3)] and are classified as invasive and non-invasive forms based on histopathologic findings. Three types are true tissue-invasive infectious diseases: acute necrotizing fungal rhinosinusitis, chronic invasive fungal rhinosinusitis and granulomatous invasive fungal rhinosinusitis caused mainly by Aspergillus flavus [(4)]. The invasive forms can be life-threatening systemic illnesses and mostly affect immunocompromised patients. The non-invasive group contains the allergic fungal rhinosinusitis (AFS) and the sinus fungus ball (SFB), developed in immunocompetent individuals [(4)]. In the literature various terms such as aspergilloma, mycetoma of the paranasal sinus, aspergillosis or chronic non-invasive fungal disease have been used interchangeably to describe SFB [(5)].

SFB is defined as a chronic infection within the lumen of a sinus cavity, usually in the maxillary antrum, characterized by histological and or mycological evidence of fungal hyphae and no microscopic evidence of fungal invasion [(6)]. The inflammatory response in the mucosa can be of variable intensity and is adjacent to fungal elements. Clinical criteria to diagnose a SFB include radiological evidence of sinus opacification with or without associated flocculent calcifications or detection of mucopurulent, cheesy or clay-like material within a sinus [(6)] (Table 1).

Table 1. Clinicopathological criteria for diagnosis of fungus ball [(6)].

1	Radiological evidence of sinus opacification with or without associated flocculent calcifications
2	Mucopurulent, cheesy or clay-like material within a sinus
3	A matted, dense conglomeration of hyphae separate from but adjacent to sinus respiratory mucosa
4	A chronic inflammatory response of variable intensity in the mucosa adjacent to fungal elements. This response includes lymphocytes, plasma cells, mast cells and eosinophils without an eosinophil predominance or a granulomatous response. Allergic mucine is absent on haematoxylin–eosin stained material
5	No histological evidence of fungal invasion of mucosa, associated blood vessels, or underlying bone visualised microscopically on Gomori methenamine silver or other special stains for fungus

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In this study we investigated the accuracy of the above defined radiological and intra-operative findings compared to histological and / or mycological results in diagnosing SFB within our institution.

PATIENTS AND METHODS

Patient analysis

All patients who underwent endoscopic sinus surgery for chronic rhinosinusitis at our institution from January 1999 through December 2006 were included.

Patients were regarded as suffering from SFB when either preoperative CT scans showed a sinus opacification with or without associated flocculent calcifications or when intra-operative findings included clay like or cheesy material within the sinus. Data from such patients was compared with the histopathological work-up, which served as the gold standard. SFB was defined according to the diagnostic criteria by de Shazo et al. [6]. This includes microscopic detection of fungal hyphae without evidence of fungal invasion of mucosa, associated blood vessels, or underlying bone visualised using Gomori methenamine silver or periodic acid Schiff (PAS) stains, in the absence of eosinophil predominance, granulomatous response, allergic mucin or Charcot Leyden Crystals on haematoxylin-eosin stains. Exclusion criteria were missing histology, invasive or allergic fungal rhinosinusitis or the diagnosis of cystic fibrosis or primary ciliary dyskinesia.

Patients with no clinical, radiological or histological signs of SFB served as controls to calculate sensitivity, specificity, PPV and NPV of radiological, surgical, histological and mycological findings.

In addition we recorded postoperative complications, follow up and outcome. All CT studies were performed using a contrast enhanced high-resolution technique. Contrast enhancement was used as in some patients clinical findings also were suggestive for a malignant disease. To have a uniform investigation this imaging protocol has been chosen in all cases. Samples were obtained by standard surgical procedures under general anaesthesia. Conventional HE, methenamine and/or PAS stains were available. Slides from the specimens were analysed independently by the pathologist and mycologist. Histopathological features such as the presence of allergic mucin, fungal colonies and inflammatory reaction in the nasal sinus mucosa, visibility of fungal hyphae and signs of invasive growth were also recorded.

Statistical analysis

All computations were performed using SPSS 16.0 for Mac. Crosstabs were used to compare different diagnostic tools by evaluating their sensitivity, specificity and predictive values. Fisher's exact test and the chi-squared test were used to detect dependencies between categorical variables.

RESULTS AND ANALYSIS

In total, 724 patients received endoscopic sinus surgery for chronic rhinosinusitis from January 1999 through December 2006 at our institution. The data from 615 patients were analyzed. In total, 109 patients were excluded due to misleading diagnostic code, histological signs of invasive or allergic fungal rhinosinusitis or other diagnosis such as cystic fibrosis or primary ciliary dyskinesia.

Ninety of 615 (15%) patients were regarded as SFB due to the radiological and/or surgical findings (Table 2).

In 53 of these 90 cases (59%), the diagnosis was confirmed by detection of fungal material through histological and/or mycological work up (51 by histology and 2 by mycology) and these cases were defined as "true" SFB (Figures 1 and 2). Eleven of 37 were clinical suggestive, but not morphologically confirmed cases of fungal infection based on retrospective methenamine silver staining.

Table 2. Distribution of SFB among all treated patients with chronic Rhinosinusitis.

	Total	CRS	**SFB**	%	confirmed diagnosis[2] (%)	%	concurrent diagnosis[1] (%)
1999	63	53	**10**	16	6	10	60
2000	67	52	**15**	22	8	12	53
2001	65	52	**13**	20	6	9	46
2002	71	58	**14**	18	4	6	31
2003	66	58	**8**	12	6	9	75
2004	107	93	**14**	13	11	10	79
2005	83	75	**8**	10	7	8	88
2006	93	84	**9**	10	6	6	67
Total	615	525	**90**	15	53	9	59

CR = chronic rhinosinusitis.

[1] based on radiological, intraoperative, histopathological or mycological findings.

[2] based on histopathological or mycologcigal confirmation of fungal material.

In 112 of 615 sinus specimens (18%) mycological analysis with HE and PAS stains was performed besides histological investigation. Of those, 81 were histologically negative and 31 histologically positive for fungae. In 17 of 31 positive cases (55%) the mycologists did not confirm the diagnosis of SFB and in 2 of 81 histologically negative cases the mycologists found fungal material. Only in 14/31 (45%) cases the pathologists and mycologists agreed in their estimation. An overview is listed in Table 3.

Table 3. Comparison between histological and mycological microscopic analysis.

	Mycology pos.	Mycology neg.	Total
Histology pos	14 (45%)	17 (55%)	31
Histology neg	2 (2%)	79 (98%)	81
Total	16	96	

The sensitivity of mycological analysis compared to gold-standard, histologically defined cases was 88%, with a specificity of 82%, and PPV of 45% and NPV of 98%. The calculated probability that the pathologists found fungal material in a case,

where the mycologists did not was 17% in our study. Our data show a moderate to strong correlation between the two investigations with a contingency coefficient of 0.677.

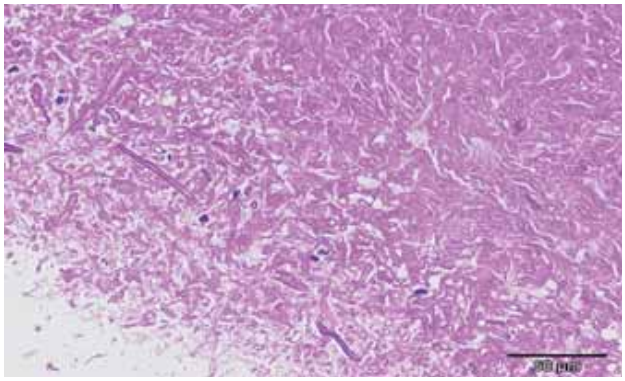

Figure 1. Isolated fungal hyphae (hematoxylin and eosin, original magnification x200).

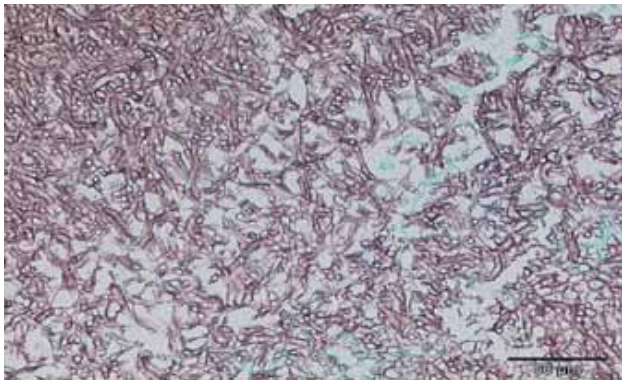

Figure 2. Tight bundles of hyphae with septae (methenamine silver, original magnification x400).

Fungus culture was carried out in 48 of all 90 SFB cases (53%) and was positive 11 times (23%) (Table 4). It showed *Aspergillus fumigatus* in 6 cases, *Penicillium* species in 4 cases and *Scedosporium apiospermum* in a single case. We compared the result of microscopic analysis and fungal growth in culture (Table 4). In 3/11 cases (27%) with positive fungal culture (one *Aspergillus fumigatus*, two *Penicillium* species) the histology was negative. In 6/11 cases (54%) with positive fungal culture (four *Aspergillus fumigatus*, two *Penicillium* species) the mycological investigation failed to demonstrate fungal material. Overall the sensitivity, specificity, PPV and NPV for fungal growth in culture compared to histology was 73%, 41%, 27% and 83% respectively. Compared to mycological results in microscopic analysis it was 45%, 69%, 31% and 81%. There was no evidence of conformity between mycological or histological result and fungal growth in culture.

In 606 of 615 cases we analysed the severity of the inflammatory reaction in correlation with the detection of fungal material. In 9 cases this differentiation could not be made due to incomplete data. Among them 51 were positive for fungal material. We distinguished between minimal, moderate and severe inflammation depending on the degree of lymphoplasmacellular infiltration. In fungal disease, the inflammatory reaction of the mucosa was minimal in 31% (16/51), moderate in 43% (22/51) and severe in 25% (13/51) of the cases. In comparison, the tissue reaction in controls was minimal in 76% (431/555), moderate in 18% (101/555) and severe in 6% (32/555) of the cases. The difference in these results was significant ($p < 0.001$).

Among the 53 patients with confirmed SFB, 31 (58%) were females and 22 (42%) were males. The ages ranged from 27 to 94 years with no statistically significant difference between the genders. The 94-year-old patient underwent endoscopic investigation for a suggested laryngeal cancer. Preoperative imaging of this otherwise healthy patient showed additionally a mass in the maxillary sinus. During the planned microlaryngoscopic investigation a sinusotomy of the maxillary sinus was also performed.

Table 4. Comparison of results of microscopic analysis and fungal growth in culture.

	Culture pos	Culture neg	Total
Histology pos	8 (27%)	22 (73%)	30
Histology neg	3 (17%)	15 (83%)	18
Total	11	37	

	Culture pos	Culture neg	Total
Mycology pos	5 (31%)	11 (69%)	16
Mycology neg	6 (19%)	25 (81%)	31
Total	11	36	

Almost all cases (51/53; 96%) were unilateral with a single sinus affected. In 30/53 (57%) the left and in 21/53 (40%) the right side was involved. The maxillary sinus was the most frequently affected 41/53 (77%) followed by the sphenoid 10/53 (19%). One of 53 cases was localized to the frontal and one to the ethmoidal sinus. Two patients had bilateral SFB (1/53 maxillary sinuses, 1/53 sphenoid sinus) but in all of these four cases there was no confirmation of fungal material in either histological or mycological work up. In 34/53 (64%) of the cases, patients complained of facial pain or maxillary pressure, in 26/53 (49%) rhinorrhoea or postnasal drip, 10/53 (19%) chronic nasal obstruction, 6/53 (11%) repeated superimposed bacterial infection and 3/53 (6%) hyposmia or epiphora. In 3/53 cases the disease was an incidental finding on CT-scan.

In 72/615 cases (12%) the radiological report was not available. Seventy-two of the remaining 543 patients (13%) had sinus opacification with or without associated flocculent calcifications on CT examination (Figure 3) and were radiologically diagnosed as SFB. In 40 of the latter 72 (56%) cases the pathological examination confirmed the diagnosis. In the remaining

32 (44%) there was no proof of fungal material in the specimen but signs for chronic inflammation. Calcification could histologically not be shown. In 8 of 72 (11%) patients there was no radiological sign of SFB but histological analysis revealed fungal hyphae in the respective sinus. The sensitivity, specificity, PPV and NPV of CT evaluation was 83%, 94%, 56% and 98% respectively.

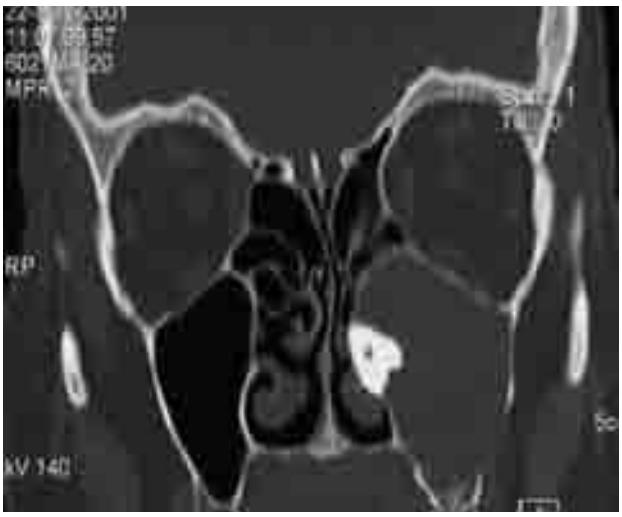

Figure 3. Computed tomographic scan of left maxillary SFB with typical sinus opcification and calcification but negative histopathological findings.

All of the 90 cases were treated with endoscopic sinus surgery. The affected region was clearly exposed and the fungal mass radically removed. Biopsy of the surrounding mucosa was performed in all patients. In 38 of 90 suspect cases (42%) histology failed to confirm fungal disease although the operative appearance had been described as the pathognomonic cheese-like, dry substance (Figure 4).

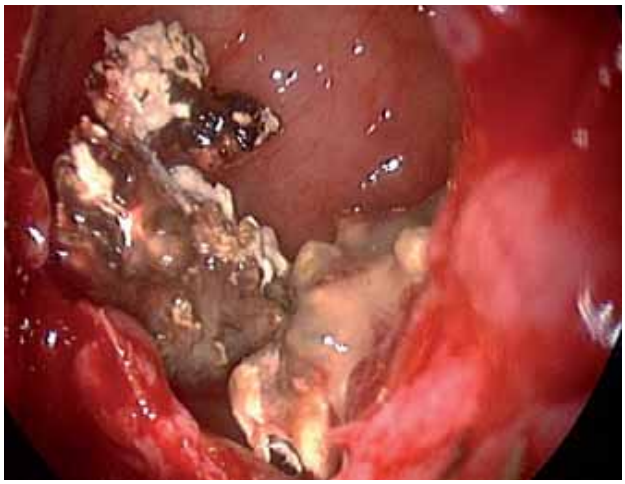

Figure 4. Gross photograph of a fungus ball taken through an endoscope with typical clay-like material but negative histopathologic findings.

As far as gross findings were concerned we calculated a sensitivity of 98%, a specificity of 93%, a PPV of 57% and a NPV of 100%. The values of PPV and NPV of the different diagnostic methods are listed in Table 5 and sensitivity and specificity in Table 6.

Table 5. Positive and negative predictive value of diagnostic methods in SFB.

	CT +	CT -	OP +	OP -	Histo +	Histo -	Myko +	Myko -
CT +	-	-	83%	1%	83%	7%	86%	31%
CT -	-	-	17%	99%	17%	93%	14%	69%
OP +	94%	3%	-	-	98%	15%	93%	37%
OP -	6%	97%	-	-	2%	85%	7%	63%
Histo +	56%	2%	57%	0%	-	-	88%	18%
Histo -	45%	98%	43%	100%	-	-	12%	82%
Myko +	32%	3%	30%	2%	45%	2%	-	-
Myko -	68%	97%	70%	98%	55%	98%	-	-

Table 6. Sensitivity, specificity, PPV and NPV of diagnostic methods in SFB.

	CT-Scan	Intra operative findings	Mycology
Sensitivity	83%	98%	88%
Specificity	94%	93%	82%
PPV	56%	57%	45%
NPV	98%	100%	98%

DISCUSSION

It has been estimated that fungal rhinosinusitis accounts for approximately 10% of SFB and makes up about 3.7% of cases requiring surgery to nose and paranasal sinuses. Similar to other studies we have shown that SFB is no longer a rare pathological diagnosis since 8% of operated patient specimens were histologically or mycologically confirmed cases of SFB. Although the diagnostic criteria defined by de Shazo et al. [3] based on clinical, radiological and histological examinations are said to be highly pathognomonic, we found that the evaluation of the radiologist and/or surgeon does not correspond well with the pathological work up for SFB. It is well known that the clinical presentation of SFB is often non-specific and as such symptoms of patients with SFB do not significantly differ to patients with chronic rhinosinusitis [2]. As in other studies [6], we frequently found superimposed bacterial infection in patients with headache, facial pain or postnasal drip. We could not find any clinical symptom specific for SFB. Large studies in France [7,8] have demonstrated that 13-20% of SFB diagnoses are incidental findings. In our series 6% (3/53) of the patients were asymptomatic and the disease was incidentally discovered.

It is generally accepted that diagnostic work up of suspected SFB cases CT is the imaging procedure of choice. According to the literature the most common CT finding, observed in about 90% of the cases is partial or complete homogenous opacification [9]. Microcalcifications or “metallic dense” spots are seen in about one third of the cases. The sensitivity and

specificity of CT imaging using the criteria defined by de Shazo et al. [6] were calculated to be 62% and 99%, respectively. According to a study by Zinreich et al. [9], 75% of the patients with chronic rhinosinusitis were correctly diagnosed by preoperative CT scan. In our study we reassessed a high number of preoperative CT scans (543) in patients undergoing endoscopic sinus surgery for chronic rhinosinusitis. Our calculated sensitivity was 83% and therefore higher than described in the literature. The calculated specificity (94% compared to 99%) and NPV (98% compared to 100%) are equivalent with the published data but the PPV (56%) is clearly lower (78%) [10]. Referring to our data and the literature [11] we can conclude that a preoperative CT scan is a good diagnostic tool to exclude a SFB, but there remains a wide differential diagnosis for positive radiological findings. According to Ahsan et al. [11] a unilateral opacification of the paranasal sinus was found only in 2.5% of all the paranasal sinus CT scans performed during 3 years in their institute (28/1118). Of those 28 cases, 13 (47%) had inflammatory and 12 (43%) neoplastic disease. Of those with neoplastic disease, 6 (50%) were malignant. Lee [12] observed in a recent study a much higher percentage (23%, 121/524) of unilateral sinus pathology in patients who had undergone sinus surgery. The greatest number of those patients had CRS followed by CRS with polyps and sinus fungus ball (18/121). Calcifications within the sinus were observed only in patients with a fungus ball (12/18 patients, 67%). In our study the radiologists could not differentiate between inflammatory or malignant disease in 16% (12/72) of the preoperative CT scans. In these cases the pathological work up did not reveal evidence for malignancy.

Gross findings of mucopurulent, cheesy or clay-like material within a sinus are considered highly suggestive of SFB [6]. In our series the calculated sensitivity and specificity was with 98% and 93% comparable to literature (100% and 99%, respectively [10]). Despite an intra-operative conviction of the diagnosis of SFB the intra-operative PPV was only 57% compared to 83% [10]. In both our survey and the study of Dhong [10] there were no false negative cases. However, both studies showed that the differentiation between a true and a false positive case was difficult. Dhong [10] encountered 11/63 (17%) cases with typical gross findings but negative pathological work up.

It remains unclear whether radiologists or surgeons often misdiagnose a chronic bacterial infection as SFB or if the pathologist and mycologists overlook fungal material during their investigation. According to the review of Grosjean et al. [2] no histological specimen should be considered to be negative for fungus unless a silver stain has been performed. Therefore we reassessed all the negative slides and retrospectively carried out methenamine silver stains, but the number of histologically proved SFB could not be increased. Mycologists routinely perform HE and PAS stains only and these were not re-evaluated in this study. PAS is said to be less sensitive than silver stains [2] which could be an explanation for the lower sensitivity and specificity of mycological work up in our series compared to histologically defined cases (Table 3). According to Taylor et al. [13], the fluorescein-labeled chitinase-staining technique has a greater sensitivity in detecting fungal organisms compared to methenamine silver staining. This method was used in cases with AFS, however we failed to find a study performing this special staining technique in SFB. Whether the diagnostic accuracy of SFB can be improved by applying this method cannot be answered with this study, but should be considered in future studies.
Other explanations for the discrepancy between clinical and histological diagnosis are either sample error or poor quality of the examined material due to inadequate transport methods or long transportation times.

According to a study by a Taxy [14], concentrations of fungal elements vary from diffuse to dense, and the dense packing of a fungus ball colony contributes to a central pallor, especially in larger colonies, which may obscure recognition of the organism. This phenomenon could also explain the different evaluation of the pathologists and the mycologists. If the outer part with higher concentration of fungal elements had been sent to the pathologist and the mycologist had only received an area with central pallor it could have lead to under diagnosis.
A severe inflammatory reaction of the surrounding tissue was evident more often in cases of SFB than in controls and thus could be an additional sign for fungal infection. In other studies the histopathological review of associated mucosa demonstrated only mild to moderate infiltration of chronic inflammatory cells [6,7] and thus our findings appear to be the first report of severe inflammation associated with fungal infection to the best of our knowledge.

The value of fungal culture in the diagnosis of fungal rhinosinusitis remains a matter of debate. The cultured fungi of Aspergillus fumigatus, Penicillium species and Scedosporium apiospermum in our study are common aetiological agents in SFB [15]. But as listed in Table 4, this result may not be reliable as there was no evidence of conformity between direct microscopy and fungal growth in culture. According to the literature [16], fungi frequently fail to thrive even in hyphae-rich material as the viability of fungal elements in fungus balls is poor. Furthermore other limitations, such as slow growth of fungi, delayed production and special nutritional requirements of certain fungi may inhibit their detection and identification. Collins et al. [16] investigated the effect of using multiple culture media for the diagnosis of fungal sinusitis and concluded that the use of different culture media influences identification from samples of fungal-like mucin. In our study the number of positive cultures was low although we routinely culture fungi on different culture media. The interpretation of positive culture results is difficult since in every case contamination must be considered. The presence of fungi in the sinus may also be

benign, colonizing normal sinuses or forming saprophytic crusts [2]. As with the isolation of bacteria in sinus cavities in these patients, the presence of fungi does not prove that these pathogens directly create or perpetuate disease.

Similar to other studies [2], SFB in our series was mostly encountered in older individuals with an average age at presentation of 64 years and a range between 14-90 years. In agreement with the literature [17], the maxillary sinus was the most frequently involved site (77%) followed by the sphenoid sinus (19%). However, SFB can occur in any sinus.

In conclusion, we can say that in spite of well-defined diagnostic criteria the diagnosis of SFB remains difficult. We suggest a high number of misdiagnoses may occur due to sampling error. It is of vital importance that the surgeon collects a representative specimen of the suspected SFB and the surrounding tissue intra-operatively and ensures the sample is correctly moistened and transported quickly to the laboratory. A parallel analysis of received specimens by a pathologist and mycologist may increase the chance of an accurate diagnosis. The presence of a severe inflammatory reaction of the surrounding tissue was in this study associated with SFB and we postulate this can be used as an additional indicator of fungal infection. Fungal culture does not contribute to a correct diagnosis. The contribution of fluorescein-labeled chitinase-staining techniques to increase the diagnostic accuracy in suspected cases of SFB could be further investigated. It could also be that bacterial infection mimicry clinical appearance of fungal sinusitis and therefore in a high number of cases no fungal material can be found in specimens. This thesis should be followed up in further prospective investigations.

To summarize, diagnostic criteria of SFB have been clearly defined and should assist in making a safe diagnosis of this condition by means of CT imaging scans and intra-operative findings. In our retrospective study application of this diagnostic approach was less than ideal. The diagnostic accuracy of radiological and intra-operative evaluation was unsatisfactory with a PPV of 56% and 57% respectively. Whether incorrect diagnoses are errors secondary to radiologists, surgeons or histological and mycological analysis is unclear. Perhaps improvements in diagnostic accuracy could be made if pathologists and mycologist analyse samples in concert and simple rules concerning correct culture and transportation of samples are followed.

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