

Extranasal infiltrative process associated with a sinonasal fungus ball: does it mean invasive fungal sinusitis?

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PURPOSE

Invasive fungal sinusitis (IFS) has rarely been reported to develop from non-IFS. The purpose of this study was to disclose the nature of the extranasal infiltrative process in the presence of a sinonasal fungus ball (FB).

METHODS

We retrospectively reviewed the medical records, computed tomography, magnetic resonance images of 13 patients with sinonasal FB and the extranasal infiltrative process. Based on histology and clinical course, we divided the extranasal infiltrative process into IFS and the nonfungal inflammatory/infectious process (NFIP). The images were analyzed with particular attention to the presence of cervicofacial tissue infarction (CFTI).

RESULTS

Of the 13 patients, IFS was confirmed in only one, while the remaining 12 were diagnosed to have presumed NFIP. One patient with IFS died shortly after diagnosis. In contrast, all 12 patients with presumed NFIP, except one, survived during a mean follow-up of 17 months. FB was located in the maxillary sinus (n=4), sphenoid sinus (n=8), and both sinuses (n=1). Bone defect was found in five patients, of whom four had a defect in the sphenoid sinus. Various sites were involved in the extranasal infiltrative process, including the orbit (n=10), intracranial cavity (n=9), and soft tissues of the face and neck (n=7). CFTI was recognized only in one patient with IFS.

CONCLUSION

In most cases, the extranasal infiltrative process in the presence of sinonasal FB did not seem to be caused by IFS but probably by NFIP. In our study, there were more cases of invasive changes with the sphenoid than with the maxillary FB.

Fungal infections of the nose and paranasal sinuses represent a spectrum of diseases ranging from benign, asymptomatic colonization to life-threatening, rhinocerebral infection (1). The classification of fungal sinusitis is ever changing but is generally categorized as either invasive or noninvasive, according to the presence or absence of fungal hyphae within the mucosa, submucosa, bone, or blood vessels of the paranasal sinuses (2, 3). Invasive fungal sinusitis (IFS) is further subdivided into acute, chronic, and chronic granulomatous IFS, among which acute IFS is the most fatal disease usually occurring in immunocompromised patients, with a reported mortality of 50%–80% (4). In contrast, the noninvasive form of fungal sinusitis is an indolent disease that has a good prognosis (5) and is subdivided into allergic fungal sinusitis and fungus ball (FB).

IFS may rarely develop from non-IFS, and a few cases have been reported on the progression or reactivation of FB into IFS (5–8). However, in this situation, it would be hard to determine the true nature of the extranasal infiltrative process on imaging studies because it is a rare event and can be seen in various diseases other than just IFS, including in the spread of infection from acute or chronic bacterial sinusitis, inflammatory pseudotumor, and skull base osteomyelitis. Nevertheless, early differentiation between IFS and nonfungal extranasal infiltrative process is critical for a better clinical outcome because the former requires urgent treatment, including systemic antifungal therapy and aggressive surgical debridement, whereas the latter can be managed with appropriate medical treatment and elective surgery (1, 2, 9–13).

We question whether or not the extranasal infiltrative process in the presence of sinonasal FB on imaging examinations actually means IFS, which has been converted from FB.

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To the best of our knowledge, no systematic analysis has been reported on this issue in the literature. Accordingly, the purpose of this study was to disclose the nature of the extrasinonasal infiltrative process in the presence of sinonasal FB by analyzing the clinical and imaging features in these patients.

Methods

Patients

This study was approved by our institutional review board, and informed consent was waived according to the requirements of a retrospective study. Between January 2005 and September 2012, a search of an electronic database registered in the Department of Radiology revealed a total of 15 patients who had sinonasal FB and extrasinonasal infiltrative process using computed tomography (CT) and/or magnetic resonance imaging (MRI) studies. Of these 15 patients, two were excluded because histology failed to identify fungus on surgical specimens, resulting in 13 patients who were included in this study, namely five men and eight women, ranging in age from 25 to 85 years, with a mean age of 63 years.

Imaging techniques

CT was performed in all patients, and MRI in 12 patients. In all patients, unenhanced CT scans were obtained in the axial plane using various helical CT scanner models at 2.5 mm to 3.75 mm section thickness. Contrast-enhanced CT, after intravenous administration of 60–100 mL of iodinated contrast material at a rate of 3 mL/s, was

also available for review in five patients. MRI examinations were performed on a 1.5 T (n=1; Signa Advantage, GE Healthcare) or 3.0 T (n=11; Intera Achieva, Philips Medical Systems) scanner using a head or neurovascular coil. In all patients, unenhanced T1-weighted spin-echo images (TR, 400–560 ms; TE, 10–14 ms; NEX, 2) and T2-weighted fast spin-echo images (TR, 2500–4500 ms; TE, 80–110 ms; NEX, 1) with or without fat saturation were obtained, followed by intravenous injection of 0.1 mmol/kg of gadopentetate dimeglumine and contrast-enhanced T1-weighted spin-echo images with or without fat saturation. Images were obtained in at least two planes with 3–4 mm section thickness and 0–0.4 mm intersection gap.

Clinical evaluation

All patients underwent endoscopic sinus surgery to remove FB from the affected paranasal sinuses, followed by various combinations of medical treatment, including antifungal agents, antibiotics, and steroids. In one patient with sphenoid sinus FB and the presumed diagnosis of inflammatory pseudotumor of the skull base, radiation therapy was also applied in addition to steroid therapy. In addition to FB, biopsy specimens were obtained at multiple sites of the sinonasal tract in all patients during surgery. After reviewing the imaging studies with radiologists, surgeons determined the biopsy sites where the possibility of elaborating the nature of the extrasinonasal infiltrative process seemed to be high, such as at the region of the defect of the bony wall of the paranasal sinus, at the region adjacent to the prominent extrasinonasal infiltrative process on imaging, and at the region showing an unusual ulceration or crust. In eight patients, one (n=6) or two (n=2) more sessions of biopsy were performed separately, after the initial histopathologic examination failed to reveal IFS. Special staining with periodic acid-Schiff and Grocott's methenamine silver was also conducted to identify any fungal organisms. The surgical specimens were inoculated into media and incubated to grow any fungi up to three weeks.

Based on the electronic medical records, we determined the clinicopathologic features, including the underlying disease if any, type of fungal organism within FB, diagnosis of extrasinonasal infiltrative process, and final clinical outcome of patients. The diagnosis of IFS was made if the histo-

pathologic and/or microbiologic examinations revealed fungus within the mucosa, submucosa, bone, or blood vessels of the sinonasal tract or at the extrasinonasal infiltrative process. If we failed to find fungus on histopathologic examination, patients were considered presumably to have a nonfungal inflammatory/infectious process (NFIP) and their clinical course was followed up. The presumed diagnosis of inflammatory pseudotumor was made when a biopsy revealed fibrous tissue with inflammatory cells, and the patient responded to steroid treatment (14). Probable sinogenic cellulitis was diagnosed if a biopsy revealed nonspecific inflammation and the antibiotics treatment was effective (15). Probable skull base osteomyelitis was diagnosed if the patient had radiologic features indicative of bone erosion and responded to antimicrobial therapy (16, 17).

Image analysis

All CT and MRI data were retrospectively reviewed by a dedicated head and neck neuroradiologist and a general neuroradiologist in consensus, both examiners having extensive practice in the field for 23 and 16 years, respectively. During image analysis, particular attention was paid to the location of FB, the presence of a defect of the bony wall of the paranasal sinus containing FB, the extent of the extrasinonasal infiltrative process, and the presence of the cervicofacial tissue infarction (CFTI). The extrasinonasal infiltrative process was defined as soft tissue stranding or swelling, which showed as an enhancement after the injection of contrast material. Thickening and enhancement of the dura mater and enlargement of the cavernous sinus with or without filling defects were also considered in the spectrum of the extrasinonasal infiltrative process on imaging. CFTI was defined as an area of lack of enhancement in and around the sinonasal tract on the contrast-enhanced T1-weighted image, as described by Seo et al. (18).

Results

The demographic data, chief complaint, underlying disease, type of fungal organism within FB, diagnosis of the extrasinonasal infiltrative process, method of treatment, and final clinical outcome are summarized in the Table. Patients most commonly presented with headache (n=8), followed by various cranial neuropathy (n=6; including decreased vi-

Main points

- Acute invasive fungal sinusitis (IFS) and fungus ball (FB) are two different disease entities within the spectrum of sinonasal fungal infections with very different prognosis and treatment options.
- When FB is combined with the extrasinonasal infiltrative process on imaging studies, the latter may result from either acute IFS or non-fungal inflammatory/infectious process (NFIP), such as inflammatory pseudotumor, sinogenic cellulitis, and skull base osteomyelitis.
- In our series, most cases of extrasinonasal infiltrative process in the presence of sinonasal FB did not seem to be caused by IFS but presumably by NFIP.
- More cases of the extrasinonasal infiltrative process were seen with sphenoid FB than with maxillary sinus FB.

Table. Summary of clinical and imaging features of 13 patients with coexisting fungus ball and sinonasal infiltrative disease

Patient no/ age (y)/sex	Chief complaint	Underlying disease	Organism	Fungus ball		Extranasal infiltrative process		Cervico- facial tissue infarction	Method of treatment	Final outcome
				Paranasal sinus involved	Bone defect	Diagnosis (presumed)	Extent			
1/67/F	Headache	Diabetes	<i>Aspergillus</i>	Maxillary	No	NFIP (IP)	Orbital apex, CS, ITF	No	Surgery, steroid, antifungal agents	CR
2/61/F	Headache, diplopia, vocal cord palsy	None	<i>Aspergillus</i>	Sphenoid	No	NFIP (IP)	Orbital apex, ITF	No	Surgery, steroid, radiotherapy	PR
3/25/F	Cheek pain	Aplastic anemia	<i>Aspergillus</i>	Maxillary	No	IFS	ITF, cheek	Yes	Surgery, antifungal agents	Died
4/46/M	Headache, ocular pain, diplopia	Diabetes	<i>Aspergillus</i>	Sphenoid	Yes	NFIP (IP)	Orbital apex, CS	No	Surgery, steroid, antifungal agents	PR
5/61/M	Headache	Diabetes	<i>Aspergillus</i>	Sphenoid	Yes	NFIP (Sinogenic SBO)	CS, pituitary fossa	No	Surgery, antibiotics	CR
6/48/F	Cheek pain	Diabetes	<i>Aspergillus</i>	Maxillary	No	NFIP (Sinogenic cellulitis)	Cheek	–	Surgery, antibiotics	CR
7/78/M	Headache, ocular pain	Diabetes	<i>Aspergillus</i>	Maxillary+ sphenoid	No	NFIP (Sinogenic SBO)	Orbital apex, CS, dura, ITF	No	Surgery, antibiotics, antifungal agents	CR
8/62/M	Headache, decreased vision, diplopia	Diabetes	<i>Aspergillus</i>	Sphenoid	Yes	NFIP (IP)	Orbital apex, CS	No	Surgery, steroid, antifungal agents	CR
9/70/F	Ocular pain	Lung cancer	<i>Aspergillus</i>	Sphenoid	No	NFIP (Sinogenic SBO)	Orbital apex, CS	No	Surgery, antibiotics	CR
10/67/F	Fever	Hodgkin lymphoma	<i>Aspergillus</i>	Maxillary	Yes	NFIP (IP)	Anterior orbit, cheek	No	Surgery, steroid, antifungal agents	CR
11/64/M	Headache, decreased vision, ptosis	Diabetes	<i>Aspergillus</i>	Sphenoid	No	NFIP (IP)	Orbital apex, CS, ITF	No	Surgery, steroid, antifungal agents	PR
12/80/F	Headache, decreased vision	Diabetes	Not specified	Sphenoid	Yes	NFIP (IP)	Orbital apex, CS, dura	No	Surgery, steroid, antibiotics	CR
13/85/F	Decreased vision, ptosis	None	<i>Aspergillus</i>	Sphenoid	No	NFIP (Sinogenic SBO)	Orbital apex, CS	No	Surgery, antibiotics, antifungal agents	Died

F, female; NFIP, nonfungal inflammatory/infectious process; IP, inflammatory pseudotumor; CS, cavernous sinus; ITF, infratemporal fossa; CR, complete recovery; PR, partial recovery; IFS, invasive fungal sinusitis; M, male; SBO, skull base osteomyelitis.

sion in four patients, diplopia in three, ptosis in two, and vocal cord palsy in one), ocular pain (n=3), cheek pain (n=2), and fever (n=1). Mean time between the onset of symptoms and the initial hospital visit was 14 weeks, ranging from three days to four months. Eleven of 13 patients had underlying diseases including diabetes (n=8), aplastic anemia (n=1), lung cancer (n=1), and Hodgkin lymphoma (n=1). In all eight patients with diabetes, the disease had been well controlled on medication. In 12 patients, the specific fungal organisms could be identified on histologic examination of FB, all of which were found to be *Aspergillus* species.

Of 13 patients, only one (7.7%) with aplastic anemia was confirmed to have IFS on histologic examination. She had

FB in the maxillary sinus and died of septic shock and acute renal failure nine days after surgery. The remaining 12 patients (92.3%) were diagnosed as presumed NFIP (inflammatory pseudotumor in seven, sinogenic skull base osteomyelitis in four, and sinogenic cellulitis in one) because there was no histopathologic or microbiologic proof of tissue invasion by the fungus and also because patients responded well to medical treatment using steroids or antibiotics. Histologic examination from the surgical specimens only revealed acute and/or chronic inflammation in these patients. In five cases of presumed sinogenic skull base osteomyelitis and sinogenic cellulitis, Gram staining and culture were performed. Only two positive cultures were obtained,

one of *Haemophilus influenza* and the other of *Staphylococcus aureus*. The low yield positive bacteriologic culture could be due to the fact that patients had been on antibiotics prior to operation. Eleven of 12 patients recovered from the symptoms either completely (n=8) or partially (n=3) during a mean follow-up of 17 months (range, 6–44 months). The remaining one patient with no underlying disease, who had FB in the sphenoid sinus, died of aspiration pneumonia associated with a poor general condition six months after surgery. Although eight of 12 patients with the diagnosis of presumed NFIP received antifungal medication for fear of the possibility of missed IFS, we considered these patients to have NFIP because it was not until the instillation of steroids or

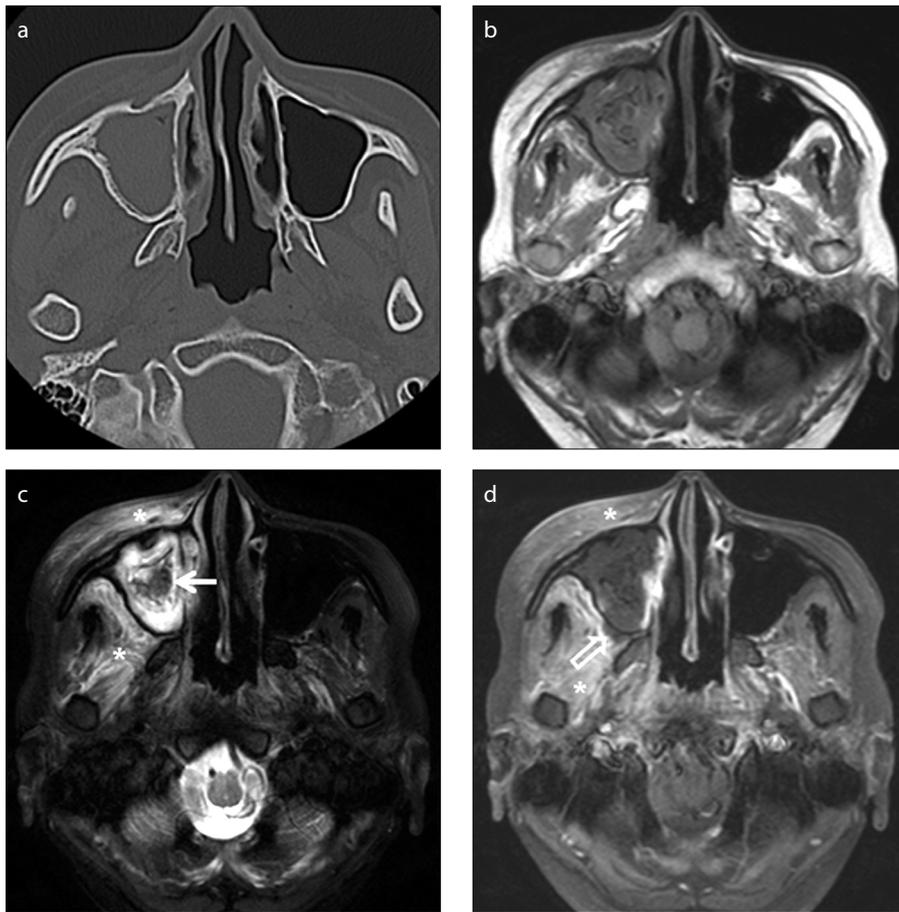


Figure 1. a–d. Patient 3. Invasive fungal sinusitis (IFS) in the presence of a right maxillary sinus fungus ball (FB) in a 25-year-old woman with aplastic anemia. Unenhanced CT scan (a) shows a total obliteration of the right maxillary sinus by soft tissue lesion. The wall of the maxillary sinus is sclerotic and significantly thickened. A CT scan just below the one shown in (a) also demonstrated punctate calcifications within the lesion (not shown). T1-weighted image (b) shows mixed isointensity/hypointensity of the entire lesion compared with the adjacent nasal mucosa. T2-weighted image (c) with fat suppression clearly shows hypointensity in the center of the lesion (arrow), which represents FB, surrounded by hyperintensity, which represents inflamed mucosa. The extrasinonasal infiltrative lesion is clearly seen in the adjacent infratemporal fossa (ITF) and anterior cheek (asterisk). Contrast-enhanced fat-suppressed T1-weighted image (d) shows no enhancement of the entire maxillary sinus except for the mucosa of the medial wall due to mucosal infarction. Note a small area of no enhancement in the ITF contiguous to the maxillary sinus lesion (open arrow), which also represents a tissue infarction caused by IFS. Also note the enhancement of the extrasinonasal infiltrative process in the ITF and anterior cheek (asterisk).

antibiotics that clinical recovery became apparent in these patients. After noticing a clinical improvement and negative fungal cultures up to three weeks, antifungal drugs were dropped from the treatment regimen in these patients.

The location of FB, the presence of a defect of the bony sinus wall, the extent of the extrasinonasal infiltrative process, and the presence of CFTI on CT and MRI are summarized in the Table. FB was located in the maxillary sinus in five patients (Fig. 1) and sphenoid sinus in nine patients (Figs. 2, 3). One patient had FB in both sinuses. A defect of the bony sinus wall associated with FB was found in five patients, of whom four

had a defect at the sphenoid sinus (Fig. 3) and one at the maxillary sinus. Various sites were involved in the extrasinonasal infiltrative process, including the orbit in 10 patients (orbital apex in nine and anterior orbit in one; Fig. 3), intracranial cavity in nine patients (cavernous sinus in nine, dura mater in two, and pituitary fossa in one; Figs. 2, 3), and soft tissues of the face and neck in seven patients (infratemporal fossa in five and anterior cheek in three; Fig. 1). Most patients with sphenoid sinus FB had the extrasinonasal infiltrative process in the orbital apex and/or cavernous sinus. CFTI was noted only in one patient with IFS. None of the other patients showed CFTI on MRI.

Discussion

Our results showed that most cases of extrasinonasal infiltrative process in association with sinonasal FB are presumably caused by NFIP and not by IFS.

Although both FB and IFS are categorized within the spectrum of fungal infections of the nose and paranasal sinus, the clinical manifestations and treatment as well as imaging findings are quite different. Sinonasal FB is a benign colonization of fungal hyphae, in which affected patients are usually immunocompetent and are either asymptomatic or have minimal symptoms, such as chronic pressure sensation (3). Treatment requires simple surgical removal with the restoration of sinus drainage. Antifungal medications are generally unnecessary and recurrence is rare (3). In contrast, IFS is an aggressive, often fatal infection of the paranasal sinus and adjacent vital organs, which predominantly involves immunocompromised patients and patients with poorly controlled diabetes (1, 3). Intraorbital, intracranial and maxillofacial extension is common. The intracranial spread of infection portends higher mortality, with up to 73% of patients dying. Prompt aggressive surgical debridement of the affected tissues and systemic antifungal therapy are the mainstay of treatment (3).

On CT scans, sinonasal FB most commonly appears as a hyperattenuating mass with punctate calcifications usually occupying a single paranasal sinus (3, 19). A single sinus is involved in 94% of the cases, while unilateral involvement is seen in almost 99% (19). The maxillary sinus is by far the most commonly involved sinus (94%), followed by the sphenoid sinus (4%–8%), ethmoid sinus (3%), and frontal sinus (2%) (19). The sensitivity of hyperattenuation on CT scans has been reported in 70%–76% of cases (20). The bony wall of the paranasal sinus usually becomes sclerotic and thickened from chronic inflammation. Sometimes, it may be expanded and thinned with focal areas of erosion from pressure necrosis, which is reported in 4%–17% of cases of FB (3, 19). Bone erosion is thought to be mainly related to the inflammatory process induced by fungal growth and possible superimposed bacterial infection (19). On MRI, FB is hypointense on T1- and T2-weighted images owing to the absence of free water. Calcifications and paramagnetic metals, such as iron, magnesium, and manganese, also generate areas of signal void on T2-weighted images (3, 20). Several radiologic findings of IFS are known in the literature. Unilateral mu-

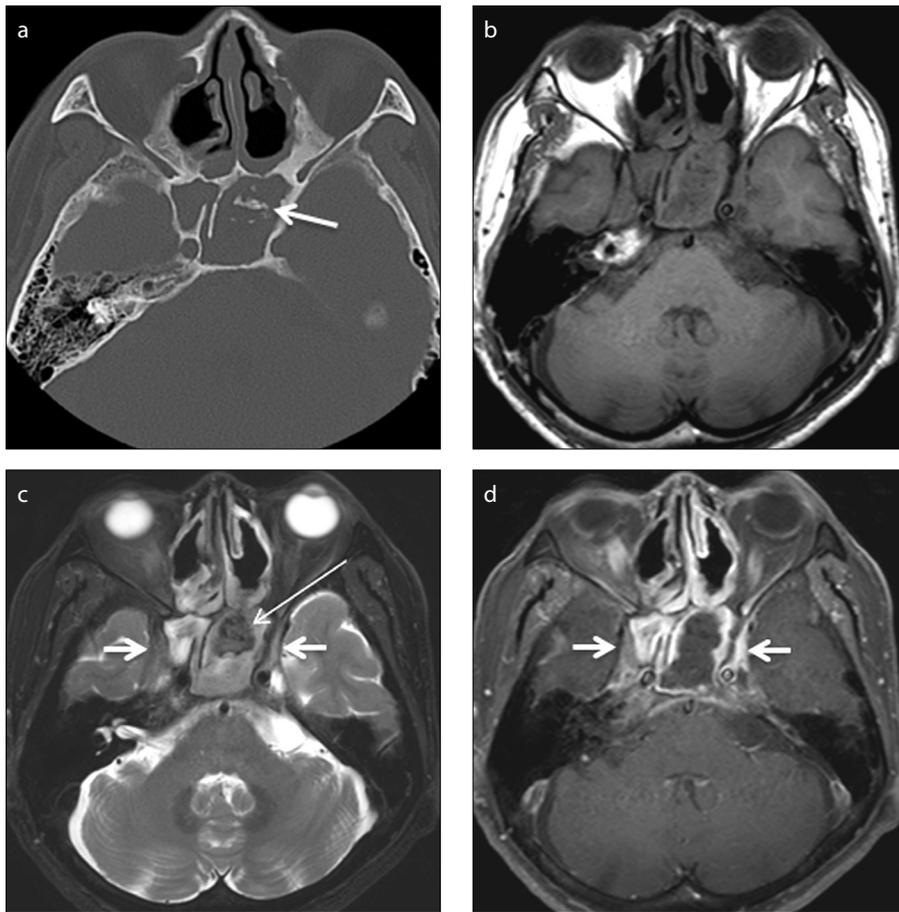


Figure 2. a–d. Patient 5. Presumed nonfungal inflammatory/infectious process in the presence of a sphenoid sinus fungus ball (FB) in a 61-year-old man with well-controlled diabetes. Unenhanced CT scan (a) shows FB with irregular calcifications in the left sphenoid sinus (arrow). The sinus wall is sclerotic and thickened. As in Fig. 1, FB is seen as a mixed isointensity/hypointensity on the T1-weighted image (b) and hypointensity on the fat-suppressed T2-weighted image (c). Contrast-enhanced fat-suppressed T1-weighted image (d) shows enhancement of the sinus mucosa without enhancement of FB and sinus secretion. T2-weighted image best separates FB (long arrow in c) from the inflamed mucosa and secretion. Note the abnormal enlargement and enhancement of bilateral cavernous sinuses (short arrows in c and d), representing the extrasinusal infiltrative process.

cosal thickening of the sinonasal tract is the most consistent, though nonspecific, early CT and MRI finding (3). Aggressive destruction of the bony sinus wall occurs rapidly with intracranial and intraorbital extension. Obliteration of the periantral fat is reported to be an early sign of extrasinusal extension of IFS (21). MRI is superior to CT in evaluating extrasinusal extension of the disease. In the brain, the progression of IFS results in meningitis, cerebritis, granulomas, cerebral abscess, cavernous sinus thrombosis, and cerebral infarction (3, 20). Recently, an area of lack of enhancement in and around the sinonasal tract on contrast-enhanced T1-weighted images, so-called CFTI, has been reported to be a characteristic MRI finding of acute IFS (18).

Chronic IFS is a slowly progressive fungal infection with a time course longer than 12 weeks (3, 10). Affected patients are usually immunocompetent, but those with a low

level of immunocompromise are also susceptible. Patients have a history of chronic rhinosinusitis (3, 20). Symptoms directly related to the invasive disease take months or even years to develop. On imaging, soft tissue in the paranasal sinus with associated sinus wall erosion is commonly seen. This may be mass-like and may mimic a sinonasal malignancy (20). It has a tendency to invade adjacent structures, such as the orbit, cavernous sinus, and intracranial cavity. Differentiation between chronic IFS and malignant neoplasm may not be possible on imaging findings (3). Chronic invasive granulomatous fungal sinusitis is a fungal infection characterized by noncaseating granulomas in the tissues (10). The disease has been primarily found in Africa and Southeast Asia and is similar clinically and radiographically to chronic IFS (3, 10, 20). Ir-

respective of the true nature of the infiltrative processes, i.e., IFS or NFIP, none of the cases in our series had imaging evidence of a mass formation, which has been reported as an important feature of chronic IFS, associated with the extrasinusal infiltrative process, except for the FB itself.

Previous reports have suggested that FB may progress into IFS (5–8). Conceivably, this can occur in patients with FB, who afterward suffer from conditions that deteriorate the host immunity, such as organ transplantation and steroid treatment (6). However, the progression of FB into IFS has also been reported in a patient without significantly altered immunity (8). Although still uncertain, this may be attributed to the location (sphenoid sinus) and long duration of FB (8). In our series, IFS in the presence of maxillary sinus FB occurred in one patient with immunosuppression, and this case may be considered a progression of FB into IFS.

Despite several reports on the progression of FB into IFS, this occurrence is reportedly rare. Various forms of NFIP with imaging features similar to IFS can coexist with FB of the paranasal sinus, including the spread of infection from acute or chronic bacterial sinusitis, inflammatory pseudotumor, and skull base osteomyelitis (1, 3, 15–17, 22, 23). Early differentiation between IFS and various forms of NFIP is critical for a good clinical outcome because management of these two conditions is quite different (1, 2, 9–13).

On imaging, bacterial sinusitis frequently shows air-fluid levels or air bubbles within the opacified paranasal sinus. New bone formation along the sinus wall can be accompanied in long-standing disease (24). Although uncommon in the era of antibiotics, the spread of bacterial sinusitis can cause soft tissue infiltration with or without bone destruction and abscess formation in the cheek, orbit, and intracranial cavity (25). Inflammatory pseudotumor is a very diverse group of conditions, characterized by acute and chronic inflammatory cells with a variable fibrous response (26, 27). On imaging, the disease may manifest as a mass or infiltrating soft tissue lesion involving the orbit, sinonasal cavity, or skull base, with or without bony destruction (23, 26–28). CT and MRI show various density and signal intensity with frequent hypointensity on T2-weighted images due to the relative lack of mobile protons within fibrotic lesions (27). The lesion enhances significantly on contrast-enhanced MRI. In our study, diabetes was observed in five of seven patients (71%) with presumed skull

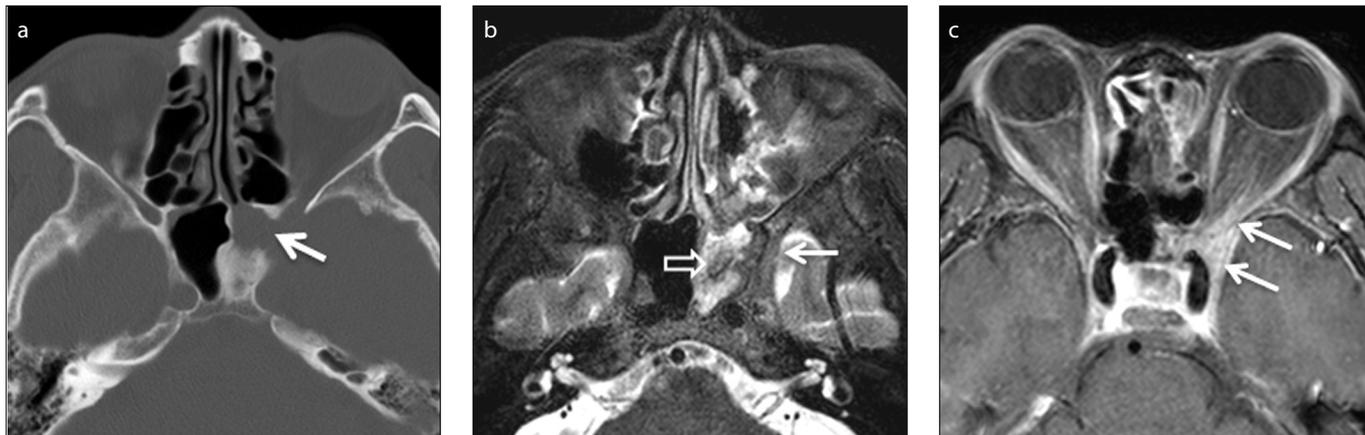


Figure 3. a–c. Patient 8. Presumed nonfungal inflammatory/infectious process in the presence of sphenoid sinus fungus ball (FB) in a 62-year-old man with well-controlled diabetes. Unenhanced CT scan (a) shows total opacification of the left sphenoid sinus. There is large defect of the sinus wall (arrow), which also shows a sclerotic change. A CT scan below the one shown in (a) demonstrated punctate calcifications within the lesion (not shown). Fat-suppressed T2-weighted image (b) demonstrates hypointense FB (open arrow) surrounded by the hyperintense inflamed sinus mucosa. Note the abnormal enlargement of the ipsilateral cavernous sinus (arrow). Contrast-enhanced fat-suppressed T1-weighted image (c) at the level of the orbital apex shows enhancement of the abnormally enlarged left cavernous sinus, which infiltrates the orbital apex (arrows), representing the extrasinonasal infiltrative process.

base pseudotumor. The results are consistent with those of previous studies, which reported that skull base pseudotumors are frequently accompanied by diabetes (28, 29). Skull base osteomyelitis usually occurs secondary to infection of the ear or paranasal sinus, especially sphenoid sinus (16, 17). Focal bone lysis, sequestrum formation, T1 hypointensity and T2 hyperintensity of bone marrow, and adjacent soft tissue infiltration are the most common imaging findings (17). Although skull base osteomyelitis can result from direct invasion by IFS itself, its possibility as the cause of the extrasinonasal infiltrative process in our series seems to be low because it carries much worse prognosis than bacterial skull base osteomyelitis (16).

Our study showed that despite a vigorous approach for obtaining adequate surgical specimens, histologic and microbiologic examinations revealed actual tissue invasion by fungal hyphae in only a minority of patients (1/13 [7.7%]) with the extrasinonasal infiltrative process in the presence of sinonasal FB. As expected, the prognosis was very grave in this situation, resulting in death of the patient immediately after diagnosis. In contrast, all of the 12 patients without histologic and microbiologic evidence of tissue invasion survived at six-month follow-up. The mean time interval of 14 weeks between the onset of symptoms and the initial hospital visit may be too long for IFS if we take the aggressiveness of IFS into consideration. Although definitive diagnosis was not made due to a lack of histo-

pathologically or microbiologically proven specific etiology as well as due to the simultaneous use of various medications for treatment, those findings may justify the diagnosis of NFIP in these patients. Our study also showed that CFTI was not recognized on MRI in any patients with a presumed diagnosis of NFIP. Considering the previous study reporting a high rate of CFTI (74% of cases) in patients with acute IFS, this may also favor the diagnosis of NFIP.

In the present study, the extrasinonasal infiltrative process was associated more commonly with sphenoid sinus FB (n=9) than with maxillary sinus FB (n=5). Considering that FB is most prevalent in the maxillary sinus, this might reflect that sphenoid sinus FB is complicated by the infiltrative process much more commonly than maxillary sinus FB. In our study, bone defect of the sinus wall was also more common with sphenoid sinus FB (n=4) than with maxillary sinus FB (n=1). Our results are in accordance with those of the previous studies (7, 31). Bone defect associated with sphenoid sinus FB has been reported in as high as 52% of cases (7). This results in exposure and subsequent potential compression of the important neurovascular structures, creating various symptoms and signs related to cranial nerve dysfunction, such as the loss of vision, diplopia, and ptosis, as seen in our patients (7, 31). However, bone defects are not always necessary for the development of clinical symptoms because infection can also spread intracranially via vascular routes around the sphenoid sinus (8).

Our study has several serious limitations. First, as described above, except for one patient with IFS, NFIP was diagnosed mostly on the basis of the clinical features in the other 12 patients. Histopathologic examination from the surgical specimens only revealed acute and/or chronic inflammation in these patients. Although we performed biopsy and microbiologic tests at multiple sites, there still remains the possibility of missing the diagnosis of IFS, particularly the chronic form of IFS. Second, our study subjects were selected through a search of the radiologic reports, in which FB was diagnosed mainly on the basis of a hyperattenuating mass with punctate calcifications in the paranasal sinus on CT. However, not all FBs have this feature, especially in cases of non-maxillary sinus FB (32), and this might have resulted in a selection bias in our study. Third, we considered the enlarged cavernous sinus with or without filling defects as an important sign of extrasinonasal infiltration on imaging. However, it may not necessarily mean the actual spread of infection into the cavernous sinus but may simply represent thrombus formation due to impaired venous drainage. The good prognosis in the majority of patients with cavernous sinus involvement in this study might support this hypothesis.

In conclusion, most cases of the extrasinonasal infiltrative process in the presence of sinonasal FB do not seem to be caused by IFS but presumably by NFIP, and its prognosis is much more favorable than IFS. In our study, there were more cases of invasive

changes with the sphenoid than with the maxillary FB.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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