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Isolated sphenoid sinus fungal mucoceles: A rare entity with a high propensity for causing neurological complications

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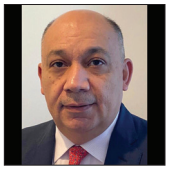

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ABSTRACT

Background: Isolated sphenoid sinus fungal mucoceles are extremely rare and potentially associated with visual disturbances, cranial nerve (CN) deficits, or pituitary dysfunction. Their initial symptoms are often absent or nonspecific, and routine examination offers little information, resulting in diagnostic and therapeutic delays. A high index of suspicion and a thorough understanding of their clinical presentation, neuroradiological features, microbiological implications, and complication profile are crucial for early diagnosis and prompt management. We, herein, analyze a series of consecutive cases of isolated sphenoid sinus fungal mucoceles whom we treated, add to the currently existing published cases, and review the pertinent literature.

Methods: From the databases of endoscopic endonasal skull base and rhinological surgical procedures maintained by our groups, all cases with isolated sphenoid sinus fungal mucoceles were retrieved and included in the study. Clinical and radiological findings, histopathologic evidence of fungal rhinosinusitis, culture results, clinicopathological designation, treatment details, and outcome of CN neuropathies were analyzed.

Results: Headache was the most common symptom (seven cases). Oculomotor (three cases) and abducens (two cases) nerve palsies were encountered in five out of eight patients. Visual loss was seen in two cases. Hypopituitarism was seen in one case. All patients underwent endoscopic endonasal wide bilateral sphenoidectomy. CN palsies improved in four out of five cases.

Conclusion: Endoscopic endonasal wide sphenoidectomy is the surgical treatment of choice and should be performed in a timely manner to prevent permanent sequelae. Histopathological and microbiological examination findings should both be obtained as they dictate the next steps of therapeutic intervention.

Keywords: Endoscopic, Fungus ball, Rhinosinusitis, Transsphenoidal, Visual

INTRODUCTION

Isolated sphenoid sinus mucoceles are relatively uncommon and represent 1–2% of all paranasal sinus mucoceles.[38,51] The subgroup of sphenoid sinus mucoceles associated with fungal rhinosinusitis (FRS) is an extremely rare condition [41,42,46,47] with only a limited number of small case series and single case reports published so far.[7,32,34,40-42,46,47,51,62] Due to the natural history and pathological anatomy of isolated sphenoid sinus mucoceles in patients with FRS, a high index

of suspicion and a thorough understanding of their clinical presentation, neuroradiological features, microbiological implications, and complication profile are crucial for early diagnosis and prompt management.

The initial symptoms of these lesions are often absent or nonspecific, and routine examination offers little information, resulting in diagnostic and therapeutic delays.[12,37] Furthermore, the sphenoid sinus is located at the center of the cranial base and is surrounded by numerous neurovascular structures, including the pituitary gland, the optic nerves, the optic chiasm, and the cavernous sinus, which harbors the oculomotor, trochlear, ophthalmic (V1) and maxillary (V2) divisions of the trigeminal, and the abducens nerves. The nerves of the pterygopalatine canal and the internal carotid arteries are also intimately related to the sphenoid sinus walls [Figure 1]. An expanding sphenoid sinus mucocele may, therefore, compress any of these structures, causing visual disturbances, cranial nerve (CN) deficits, or pituitary dysfunction.[6,11,63,65,70,71,75]

In one recently published large study of radiologically identified isolated sphenoid sinus opacifications, it was demonstrated that clinicians generally underestimated the risks of sphenoid sinus disease.[3] A more widespread awareness of this entity is obviously required so as to control its associated neurological complications preemptively. In the present study, we analyze a series of consecutive cases of isolated sphenoid sinus fungal mucoceles whom we treated, add to the currently existing published cases, and review the pertinent literature. Despite the limited number of patients included, the case series we present herein is, to the best of our knowledge, the largest reported in English literature.

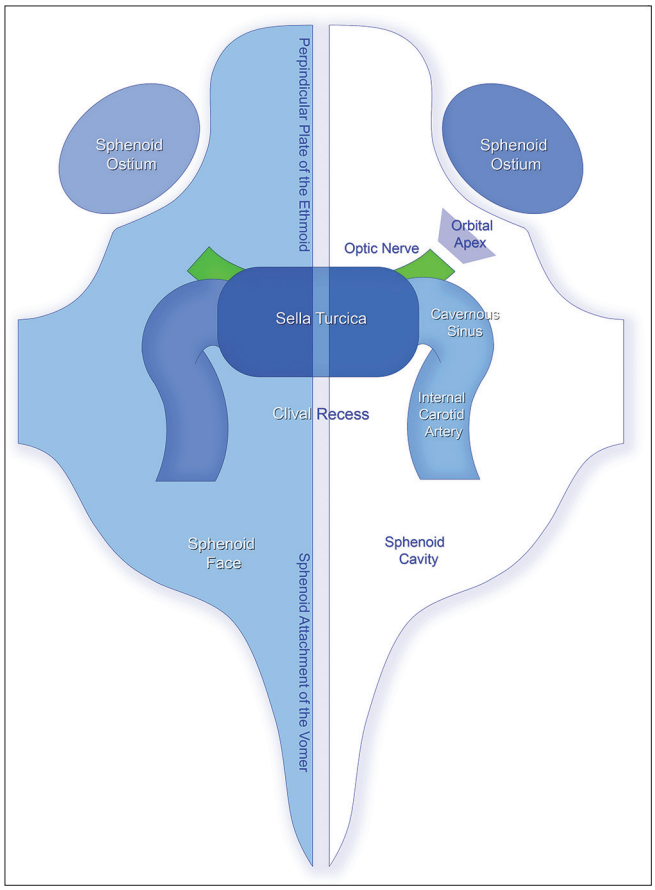

Figure 1: The sphenoid sinus is surrounded by numerous neurovascular structures that may be compressed by an expanding sphenoid sinus mucocele.

MATERIALS AND METHODS

From the databases of the endoscopic endonasal skull base and rhinological surgical procedures maintained by our groups since the year 2015, all cases with isolated sphenoid sinus fungal mucoceles were retrieved and included. Cases of isolated sphenoid sinus bacterial mucoceles were excluded from the study. Medical charts, diagnostic imaging findings, histopathology and microbiology results, and operative notes and videos were retrospectively reviewed.

For all patients, demographic data, duration of mucocele-related symptoms, clinical findings, histopathologic evidence of FRS, fungal culture results, clinicopathological designation, surgical and medical treatment details, and clinical outcome of CN neuropathies were analyzed.

Two forms of fungal sinonasal infection that may result in sphenoid sinus mucocele formation include fungus ball (FB) and allergic FRS (AFRS). FB is an extra-mucosal mycotic proliferation that completely or partially fills a paranasal sinus and is usually associated with minimal mucosal inflammation.[49,53] The pathogenesis of AFRS is not yet fully understood. Although previously considered a type I hypersensitivity reaction to fungi, the condition is currently believed to represent a host reaction to fungal proteins.[39,49]

All cases of FB were diagnosed according to deShazo *et al*. criteria,[16] [Table 1], and all cases of AFRS were diagnosed according to Bent and Kuhn criteria,[5] [Table 2], except for the presence of type I hypersensitivity to fungal allergens and asthma. No statistical analysis was conducted due to the small sample size.

RESULTS

Demographics and clinical findings

Eight patients with a diagnosis of isolated sphenoid sinus fungal mucoceles were retrieved and included in the analysis. The patient population consisted of five males and three females, with an age range between 26 and 73 years (Mean age 47.6). The duration of mucocele-related symptoms ranged between 4 and 24 months. CN palsies included oculomotor

Table 1: The deShazo criteria for diagnosis of a fungus ball (FB).

1. Radiologic 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 mucin is absent on hematoxylin-eosin-stained material.
5. No histologic evidence of fungal invasion of mucosa, associated blood vessels, or underlying bone visualized microscopically on Gomori methenamine silver or other special stains for fungus.
After deShazo *et al*. 1997.

Table 2: Bent and Kuhn criteria for diagnosis of allergic fungal rhinosinusitis (AFRS).

1. Type I hypersensitivity confirmed by history, skin tests, or serology
2. Nasal polyposis
3. Characteristic CT signs
4. Eosinophilic mucus without fungal tissue invasion
5. Positive fungal stain
6. Asthma
7. Unilateral predominance
8. Radiographic bone erosion
9. Positive fungal culture
10. Charcot-Leyden crystals
11. Peripheral eosinophilia
After Bent and Kuhn, 1994.

nerve palsy observed in three cases and abducens nerve palsy observed in two cases. Visual loss was seen in two cases. Headache was the most common symptom and was present in seven cases. FB was diagnosed in three patients and AFRS in four patients. CN palsies improved in four out of five cases. Hypopituitarism manifesting as central hypothyroidism (low levels of thyroid-stimulating hormone [TSH], T4) and low adrenocorticotropic hormone (ACTH) and serum cortisol levels were seen in one case.

Neuroradiological investigations

All patients had radiological findings consistent with isolated mucocele formation within the sphenoid sinus. Computed tomography (CT) scans revealed opacification and expansion of the sphenoid sinus, with variable degrees of bone erosion in all cases. Compression of the ethmoid sinuses, anterior cranial base, sellar floor, medial orbital wall, or orbital apex was also seen in some cases. Magnetic resonance imaging (MRI) further demonstrated an iso- to slightly hyper-intense signal of the fluid content and a hypointense signal of the fungal balls. Areas of mixed signal intensity where small foci of T2 hyperintensities are detected within an otherwise uniform T1 isointense signal were seen in 2 cases. No enhancement of the mucoceles was seen after contrast injection. Peripheral enhancement was seen in three cases and corresponded to the contrast uptake by the mucosa of the sinus.

Treatment modalities

All patients underwent endoscopic endonasal wide bilateral sphenoidectomy. Dexamethasone was administered only to patients with neurological deficits and tapered down over 2 weeks postoperatively. Fungal cultures were performed in three out of the eight patients included and were positive in only one patient in whom *Aspergillus fumigatus* was isolated.

Outcome

Visual loss improved in all patients after surgery. Except in one patient with abducens nerve palsy, all CN palsies recovered within a maximum of 6 weeks postoperatively. Table 3 summarizes the included patients' demographics, clinical and laboratory findings, and surgical and medical treatment options used. Representative pre-and post-operative imaging and intraoperative findings from Case No. 4 are demonstrated in Figure 2.

DISCUSSION

Clinical features of isolated sphenoid sinus fungal mucoceles

At the early stages of their development, sphenoid sinus mucoceles are often asymptomatic.[43] They develop chronically and gradually expand, ultimately resulting in resorption and sometimes erosion of the bony walls of the sinus. The initial symptoms are, therefore, often nonspecific [38,60], leading to a diagnostic delay. This is in congruence with our findings, where time intervals between the onset of first symptoms and diagnosis ranged from 4 to 24 months and is similar to many other published series of isolated sphenoid fungal mucoceles.[32,41,47,62] Subsequently, a variable clinical presentation ensues and depends on the direction of mucocele extension toward the neurovascular structures in the close vicinity of the sinus walls.[43,51,63]

In addition to the sinonasal symptomatology associated with chronic FRS, the specific clinical findings reported in patients with isolated sphenoid fungal mucoceles include headache, blurring of vision, variable degrees of unilateral or bilateral visual loss, optic disc pallor, retro-orbital pain, diplopia, and abducens nerve palsy,[32,34,40-42,47,51,62] [Table 4]. Apart from oculomotor nerve palsy, which we observed in three out of

Table 3: Summary of patients included in the current study.

Case No.	Age (Years), Sex	Duration (Months)	Clinical findings	Histopathologic evidence of FRS	Fungal culture	Clinicopathological designation	Treatment	Outcome of CN neuropathy
1	73 F	12	Headache Bilateral progressive visual loss (more Lt.) Lt. oculomotor nerve palsy	Fungal Hyphae (Septate, branching at acute angles)	No	FB Mucocele	Endoscopic wide bilateral sphenoidectomy Dexamethasone	Full recovery in 6 weeks
2	60 F	8	Headache Lt. abducens nerve palsy Hypopituitarism (low TSH, T4, ACTH, serum Cortisol)	Necrotic avascular yellow cheesy material ? Fungal elements in mucin	- VE	? Chronic invasive non-granulomatous features ? AFRS Mucocele	Endoscopic wide bilateral sphenoidectomy Dexamethasone Amphotericin B	No recovery
3	58 M	6	Nasal symptoms Headache Rt. oculomotor, Rt. abducens nerve palsies	B-K +VE	Aspergillus fumigatus	AFRS Mucocele	Endoscopic wide bilateral sphenoidectomy Dexamethasone	Full recovery in 4 weeks
4	32 M	4	Nasal symptoms Bilateral progressive visual loss Lt. oculomotor nerve palsy	B-K +VE	No	AFRS Mucocele	Endoscopic wide bilateral sphenoidectomy Dexamethasone	Full recovery in 4 weeks
5	58 F	7	Headache	Fungal Hyphae (Septate, branching at acute angles)	No	FB Mucocele	Endoscopic wide bilateral sphenoidectomy	NA
6	44 M	13	Headache Intermittent diplopia	Fungal Hyphae (Septate, branching at acute angles)	-VE	FB Mucocele	Endoscopic wide bilateral sphenoidectomy	Full recovery in 1 week
7	30 M	6	Nasal symptoms Headache	B-K +VE	No	AFRS Mucocele	Endoscopic wide bilateral sphenoidectomy Dexamethasone	NA
8	26 M	24	Nasal symptoms Headache	B-K +VE	No	AFRS Mucocele	Endoscopic wide bilateral sphenoidectomy Dexamethasone	NA

AFRS: Allergic fungal rhinosinusitis; B-K: Bent and Kuhn criteria; F: Female; FB: Fungus ball; M: Male; NA: Not applicable; No: Not obtained; -VE: Negative; +VE: Positive, FRS: Allergic fungal rhinosinusitis, ACTH: Adrenocorticotropic hormone, T4: Thyroxine, TSH: Thyroid stimulating hormone, ACTH: Adrenocorticotrophic hormone, CN: Cranial nerve

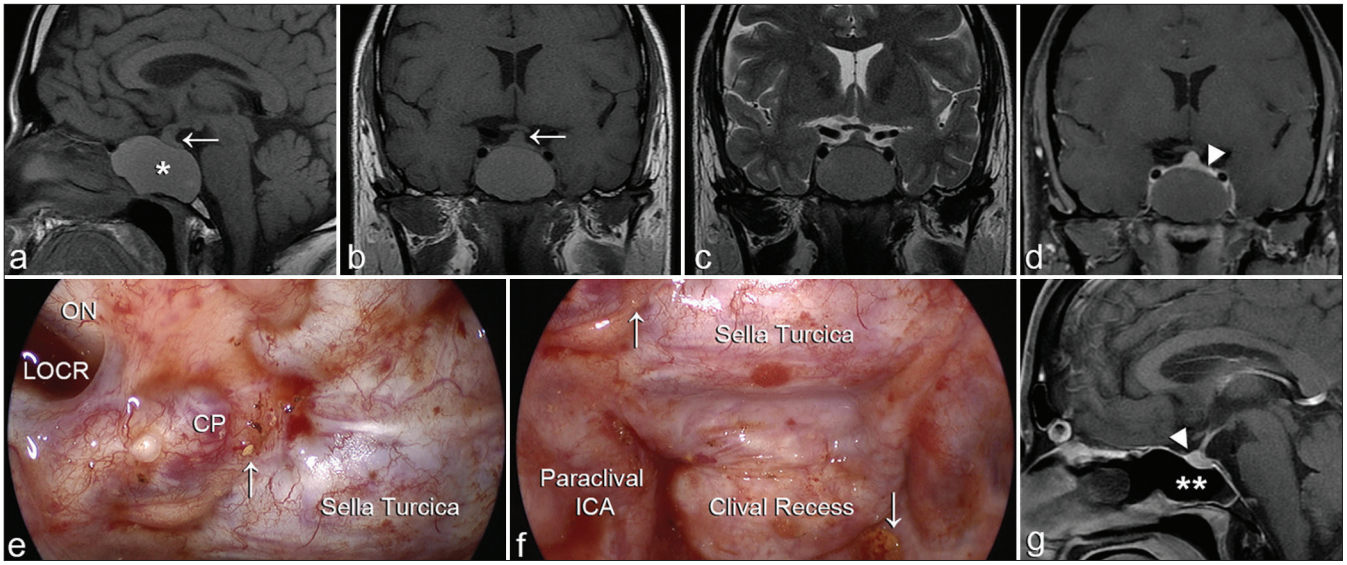

Figure 2: Isolated sphenoid sinus fungal mucocele (Case No. 4). (a-d) Preoperative magnetic resonance imaging (MRI) reveals an expansile sphenoid sinus mass (an asterisk) that displays a slightly hyperintense signal on T1-weighted (a and b), and (c) an isointense signal on T2-weighted MRI. (d) No enhancement is seen after contrast injection. Compression of the pituitary gland (a and b arrows, d arrowhead) is notable due to the mass effect of the mucocele. (e-f) Intraoperative views during mucocele marsupialization and drainage through an endoscopic endonasal transsphenoidal sphenoidectomy. Anatomical landmarks within the sphenoid sinus are seen. Yellow tiny fungal material is seen attached to the walls (arrows). (g) Postoperative sagittal T1-weighted MRI with contrast demonstrating full decompression of the mucocele and evacuation of its contents (double asterisks). The decompressed pituitary gland is seen (arrowhead). CP: Carotid prominence, LOCR: Lateral optico-carotid recess, ON: Optic nerve.

eight cases, a similar constellation of findings was seen in our series.

Although oculomotor nerve palsy is well documented in cases of sphenoid mucoceles of non-fungal etiology,[47,59,69] it was not reported in cases of isolated sphenoid fungal mucoceles. In our series, two cases of pupil-sparing (Cases No. 1, 3) and one case of non-pupil-sparing (Case No. 4) oculomotor nerve palsy were encountered. Pupillary sparing in oculomotor nerve palsy is believed to result from microvascular circulation impairment (ischemia) that involves only the central part of the nerve and spares the peripherally located parasympathetic fibers supplying the iris sphincter.[43,69] Nevertheless, pupillary involvement has been reported in 14–32% of cases of oculomotor nerve palsy resulting from a microvascular ischemic insult.[33] In contrast, oculomotor nerve palsy resulting from compressive lesions commonly presents with both ocular motility disturbance and iridoplegia.[43] Despite their compressive nature, sphenoid sinus mucoceles presenting with pupil-sparing oculomotor nerve palsy have been observed, probably due to additional mechanical forces that impair the microvascular supply to the nerve with consequent ischemia.[1,43,48] In one of our patients (Case No. 1), the oculomotor nerve palsy was initially intermittent. Friedmann and Harrison reported two similar patients in whom oculomotor nerve palsy characterized by transient drooping of the eyelid and diplopia were observed.[22] Notably, however, acute onset of CN dysfunction is the more common scenario.[12] An acute onset of oculomotor (Case No. 4) and abducens (Case No. 2) nerve palsies was also observed in two of our patients.

Extrapolating from the literature on isolated sphenoid mucocele of non-fungal etiology, oculomotor nerve involvement has been reported to represent around 70% of ocular palsies and is more frequent than trochlear and abducent nerve palsies,[22] although isolated oculomotor palsy is very rare in these cases.[43]

Visual loss was observed in two of our eight cases and was progressive in course [Figure 3]. Similar findings have been reported in the previous case reports of isolated sphenoid fungal mucoceles.[47,62] It is postulated that visual loss in sphenoid disease may be caused by compression of the optic nerve or chiasm or, to a lesser extent, by optic neuritis.[60,63]

In our series, seven out of eight patients complained of headaches that almost spanned the whole duration of the clinical history, findings that are similar to those in other reported cases.[7,32,34,40,41,47,51] In general, headache is the most common symptom of an isolated sphenoid sinus mucocele, is seen in around 70–80% of patients [27,51] and may be retro-orbital or involve the vertex.[37]

We encountered one case of hypopituitarism (Case No. 2) in our series. Hormonal profile evaluation revealed low levels of TSH, T4, ACTH, and serum cortisol. Extensive invasion of the clivus, sellar floor, sellar dura, and pituitary gland

Table 4: Isolated sphenoid sinus fungal mucocele case series published in the last 30 years.

Reference	AgeSex	Symptom duration	Clinical findings	Radiological findings	Type of FRS	Histopathological evidence	Fungal culture	Surgery	Medical treatment	Outcome
Lee *et al.*, 2002	Case No. 1 53 F	Several months	Headache Postnasal discharge	CT Soft tissue density expanding the sphenoid sinus	AFRS	Yes	No	Transseptal sphenoidotomy	-	Imp.
	Case No. 2 39 F	NR	Headache Lt. facial pressure Nasal congestion.	CT Opacification and expansion of the left sphenoid sinus	FB	Yes	-ve	Caldwell-Luc antrostomy, transnasal, transantral ethmoidectomy, and sphenoid sinusotomy	-	Imp.
	Case No. 3 71 M	NR	Anosmia Nasal congestion	CT, MRI Expansile lesion in the sphenoid sinus with bony erosion	FB	Yes	No	Endoscopic bilateral ethmoid, maxillary, and sphenoid sinusotomies	Topical nasal steroid	Imp.
	Case No. 4 59 F	Long history	Nasal polyposis Previous endoscopic sinus surgery	CT Opacification and expansion of the sphenoid sinus with bony discontinuity along the periphery. MRI T1-, T2 – Hypointensity (inspissated mucus and high protein) , Heterogeneously enhancing soft tissue mass Marked expansion of the sinus and bowing of the floor inferiorly.	AFRS	Yes	Alternaria	Endoscopic marsupialization	Topical nasal steroids for 1 Yr.	Imp.
	Case No. 5 70 F	NR	Headache Purulent rhinorrhea.	CT Opacification and some expansile changes in the left sphenoid sinus	FB	Yes	-ve	Endoscopic ethmoid, maxillary, and sphenoid sinusotomies.	Topical nasal steroid for 3 Mo	Imp.
	Case No. 6 25 F	2 Yr.	Chronic rhinosinusitis	CT Opacification of the sphenoid sinus with bowing and erosion of the sinus walls.	AFRS	Yes	No	Bilateral endoscopic ethmoid, maxillary, and sphenoid sinusotomies.	-	Imp.

(Contd...)

Table 4: *(Continued)*

Reference	AgeSex	Symptom duration	Clinical findings	Radiological findings	Type of FRS	Histopathological evidence	Fungal culture	Surgery	Medical treatment	Outcome
Campbell *et al.*, 1994	57 M	NR	Headache Nasal congestion Dec. smell, taste Diplopia Lt. Abducens palsy.	CT Expansion of sphenoid sinus without erosion Hyperdense content MRI Signal void	Cyst Fluid	Yes			-	
Naik *et al.*, 2021	32 F	1 Mo. .	Headache Dizziness Intermittent LOC Lt. Abducens	CT -Expansile mass -Erosion of clivus, Lt. petrous apex MRI -Peripheral enhancement -Central T2 hypointensity	FB	Yes	Scedosporium apiopermum	Wide endoscopic sphenoidectomy	Voriconazole 6 weeks	Imp.
Mishra *et al.*, 2022	43 F	1 Yr.	Headache Retro orbital pain Nasal blockage Lt. facial numbness Lt. Progressive diminution of vision		FB	Yes		Trans-nasal endoscopic sphenoidotomy	-	Imp.
Lee *et al.*, 2012	62 F	NR	NR	CT -Large, expansile, low-attenuation mass in the sphenoid sinus, broken into the Lt. infratemporal fossa. -Subtle, high-density material containing calcifications MRI high T1- and intermediate T2- multi-lobulated, expansile, nonhomogeneous sphenoid sinus mass, T2-hypointense signal.	FB	Yes	No	Widening of the mucocele wall via endoscopic sphenoidotomy and trans-pterygopalatine fossa approach	-	NR

(Contd...)

Table 4: *(Continued)*

Reference	AgeSex	Symptom duration	Clinical findings	Radiological findings	Type of FRS	Histopathological evidence	Fungal culture	Surgery	Medical treatment	Outcome
Smith *et al*., 2007	57 M	18 Mo.	Rt. blurred vision. Rt. Severe visual loss Rt. Pale optic disc Low Testosterone, elevated FSH, other hormones normal	CT Contrast enhancing large solid mass MRI -Mass enters the pituitary fossa with mass effect on the right optic nerve. -T1-, T2- hypointense signal	FB	Yes	Curvularia lunata (Enterobacter aerogenes)	Stereotactic transsphenoidal resection	Amphotericin B Voriconizole	Imp.
Lasardo *et al*., 2022	73 M	7 D.	Headache Diplopia Rt. Abducens palsy	CT Expanded sphenoid sinus, filled with Non-enhancing low attenuation material MRI -Sphenoid sinus expansion, impinging on the right optic canal and right SOF with displacement of CS and Rt. ICA. -Fluid signal hypointense on T1, hyperintense onT2, with peripheral enhancement.	Fungal mucin	Yes	No	Endoscopic Wide sphenoidotomy and posterior septectomy	-	NR
Ishibashi and Kikushi, 2001	81 F	2 Mo.	Headache Diplopia Lt. Abducens palsy	MRI Expanded Lt. sphenoid sinus, Hyperintense signal with central T1-, T2- hypointense signal.	Granulation tissue containing Aspergillus. (Non-invasive sphenoid Aspergillosis)	Yes	No	Endoscopic transnasal sphenoid approach	-	Imp.
Kim and Lee, 2019	51 F	NR	NR	MRI Hypointense signal on T1- and T2-weighted images surrounded by a high T1- and T2 signal.	FB	Yes	No	FESS	-	NR

F: Female; FB: Fungus ball; M: Male; NA: Not applicable; No: Not obtained; -VE: Negative; +VE: Positive, Mo: Month, Yr: Year, D: Day, MRI: Magnetic resonance imaging, CT: Computed tomography, FESS: Functional endoscopic sinus surgery, CS: Cavernous sinus, ICA: Internal carotid arteries, AFRS: Allergic fungal rhinosinusitis, Imp.: Improved, SOF: Supra-orbital fissure, NR: Not reported

was evident during surgery, with features of chronic non-granulomatous inflammation seen on histopathological examination. We speculate that mixed features of AFRS and chronic non-granulomatous FRS did concomitantly exist in this patient [Figures 4-6]. In the literature, cases of AFRS in association with pituitary dysfunction presented only with hyperprolactinemia (stalk section effect) due to compression of the pituitary gland.[10,33] Actual invasion of the pituitary tissue has previously been reported as a rare complication of invasive FRS but not in the context of non-invasive FRS.[54]

Neuroradiology of isolated sphenoid sinus fungal mucoceles

Neuroimaging is essential to disclose the pathoanatomical details of isolated sphenoid sinus fungal mucoceles. CT reveals sinus opacification and sinus bony wall expansion and erosion, and MRI provides details of the signal intensities of the mucocele contents and involvement of the optic nerve, optic chiasm, pituitary gland, and cavernous sinus.[60] Mucoceles exhibit variable imaging features on CT and MRI depending on their water and protein content, inspissation, and the presence of a superadded infection.[38,44] However, the content is often characterized by low attenuation on CT, low signal intensity on T1-weighted, and high signal intensity on T2-weighted MRI due to its high water content. Mucoceles do not enhance after contrast injection, and only marginal enhancement may be seen in some cases,[40,63] a radiological hallmark that makes the preoperative diagnosis of a sphenoid mucocele a relatively straightforward task.[30,74]

T2-weighted MRIs are particularly important to differentiate between the hypointense fungal elements and the hyperintense signal of mucosal swelling or low-protein mucous retention.[42] An FB displays a low or intermediate signal intensity on T1-weighted images and a hypointense signal on T2-weighted images.[19,32] Neuroradiological findings in all patients in our series were consistent with the features mentioned above. Demonstration of these findings should prompt surgical intervention even in those who present with only headaches or sinonasal symptoms so that potential neurological deficits are prevented.

FRS and mucocele formation

Fungal infections of the paranasal sinuses represent a disease spectrum ranging from colonization to invasive rhinosinusitis.[17,68] Colonization of the sinuses with fungi is not a rare phenomenon and does not necessarily result in an infection. The immune status of the individual often dictates whether atmospheric fungal elements lead to FRS.[17,25]

FRS is broadly classified as either non-invasive or invasive. Non-invasive sinonasal fungal diseases include saprophytic fungal infestation (SFI), FB, and AFRS. The invasive forms of FRS include acute invasive FRS, chronic invasive FRS, and chronic granulomatous invasive FRS.[17,49] Across the literature, only non-invasive forms of FRS have been reported in cases of isolated sphenoid sinus fungal mucoceles.[7,32,34,40-42,47,51,62] In our series, mucocele formation was associated with non-invasive FRS (an FB or AFRS) in seven out of eight cases.

SFI is traditionally described as fungal colonization of the secretions of the sinonasal cavity or crusted mucosa, mostly in patients with a history of previous sinus surgery. It is the least common form of FRS described in the literature and is thought to precede the development of an FB.[8,17,49] In one of our cases (Case No. 5), SFI seems to have resulted in FB formation. The patient had a history of transsphenoidal surgery for resection of a pituitary adenoma almost 30 years before the current presentation.

FB is an extra-mucosal mycotic proliferation that completely or partially fills a paranasal sinus and is usually associated with minimal mucosal inflammation.[49,53] The diagnosis is based on the clinicopathological criteria proposed by deShazo *et al*.[16] [Table 1] Although the most commonly isolated pathogens belong to *Aspergillus* species (commonly *A. fumigatus*), fungal cultures are often negative,[15,26,29] and in only 23–50% of cultures can a fungus be grown.[20] This is probably related to the poor viability of fungal elements in the FB.[29] Other fungi occasionally cultured include *Aspergillus flavus*, *Aspergillus niger* or *Aspergillus terrus*,[21,29] *Scedosporium apiospermum* (*Pseudallescheria boydii*),[36] and *Pleurophomopsis lignicola*.[29,52] On endoscopic inspection, an FB is characteristically viscid, friable, and cheesy material, which may be green, yellow, brown, or black, and is easily peeled off the sinus mucosa, which may appear normal, edematous, or hypertrophic. FBs may partially or fill the sinus cavity. Occasionally, an FB as small as 5 mm in diameter may cause symptoms.[29] Similar intraoperative findings were observed in all of our cases with FBs. FBs seem to be a form of FRS that is frequently associated with isolated fungal sphenoid mucoceles. In our series, three cases of FB were encountered. In the case series by Lee *et al*., FB was diagnosed in three out of six patients with isolated fungal sphenoid sinus mucocele [41] and was also described in the majority of the single-case reports of isolated fungal sphenoid mucocele.[34,42,47,51,62]

AFRS is diagnosed according to the original Bent and Khun criteria.[5] [Table 2] Classically, it is necessary to meet the major criteria, which include the presence of polyps in the nasal cavity, fungi on staining, eosinophilic mucin without fungal invasion into the sinus tissue, a characteristic CT scan picture, and type I hypersensitivity to fungal allergens. Minor criteria, on the other hand, include the presence of eosinophil-rich allergic mucin and the absence of immunodeficiency or diabetes.[39] However, it was more recently shown that not all patients with AFRS have systemic

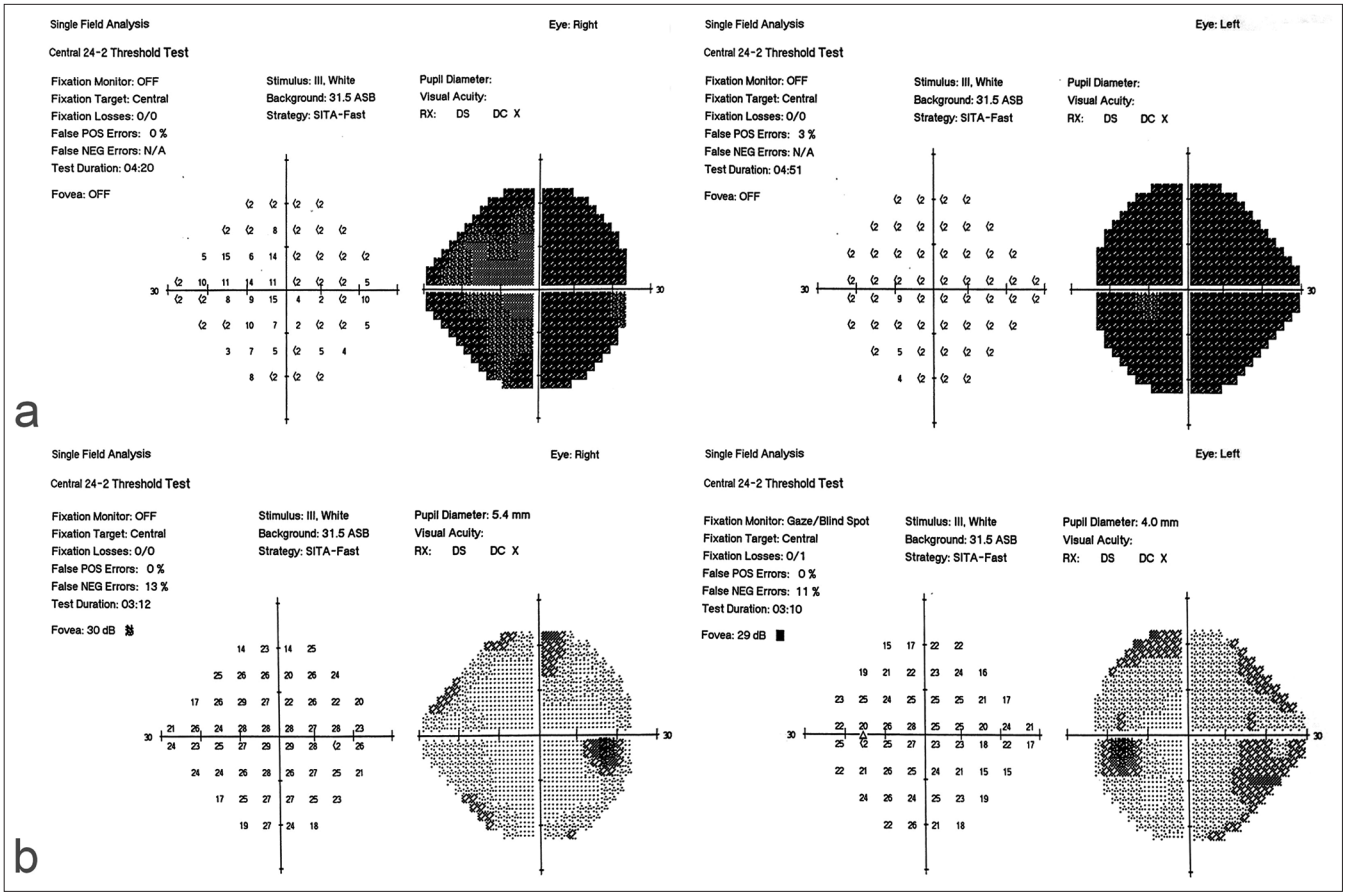

Figure 3: Visual field test (a) before and (b) after surgery (Case No.1).

(or even local) hypersensitivity to fungi [49] and that fungi induce the production of eosinophil-attracting Th2 cytokines, with the subsequent inflammatory reaction being responsible for the formation of eosinophilic (allergic) mucin.[55,61]

The pathogenesis of AFRS is not yet fully understood. Although previously considered a type I hypersensitivity reaction to fungi, the condition is currently believed to represent a host reaction to fungal proteins.[39,49] Host and environmental factors, including exposure to fungi, lead to predominantly type 2 immune responses, which encompass both adaptive responses involving TH2 cells and innate responses involving Type 2 innate lymphoid cells (ILC2s). Interleukin-5 (IL-5) from both TH2s and ILC2s induces eosinophilia, and IL-4 and IL-13 (ILC2s, TH2s) induce local immunoglobulin (Ig)E production, including antifungal IgE. Sinonasal colonization with fungi and bacteria leads to activation of the epithelium with consequent apoptosis of epithelial cells, loss of epithelial barrier integrity, and release of upstream proinflammatory chemokines and cytokines with increased thymic stromal lymphopoietin, IL-25, and IL-33 levels, and impaired fungal clearance. Recently, IL-33 has been found to be an important contributing factor in mast cell activation in patients with AFRS. Ultimately, high total and fungus-specific serum IgE levels, eosinophil-rich mucus (allergic mucin), nasal polyps, and mucosal edema and obstruction take place. Altered inflammatory responses may also involve pattern recognition receptors, including Toll-like receptors (TLRs), NOD-like (nucleotide-binding oligomerization domain-like) receptors, and protease-activated receptors (PARs).[2,4,9,18,64] The most common etiologic agents in AFRS include hyaline molds (*Aspergillus* and *Fusarium*) and dematiaceous fungi (*Bipolaris*, *Curvularia*, *Exserohilum*, *Alternaria*, *Drechslera*, and *Helminthosporium*).[28,31,64] In four out of eight patients in the current series, AFRS was the underlying subcategory of FRS that is involved in the development of isolated sphenoid sinus fungal mucoceles.

Although isolated sphenoid fungal mucoceles have been exclusively reported in patients with non-invasive FRS, in one of our patients (Case No. 2), necrotic avascular yellow cheesy material was intraoperatively seen to invade the dura mater, clival bone, petrous apex, sella turcica, and pituitary gland. Fungal elements were suspected on histopathological examination of the associated mucus within the sphenoid sinus. The patient had a past medical history of bronchial asthma. Nasal polyps were seen during surgery. In our opinion, mixed features of AFRS and chronic

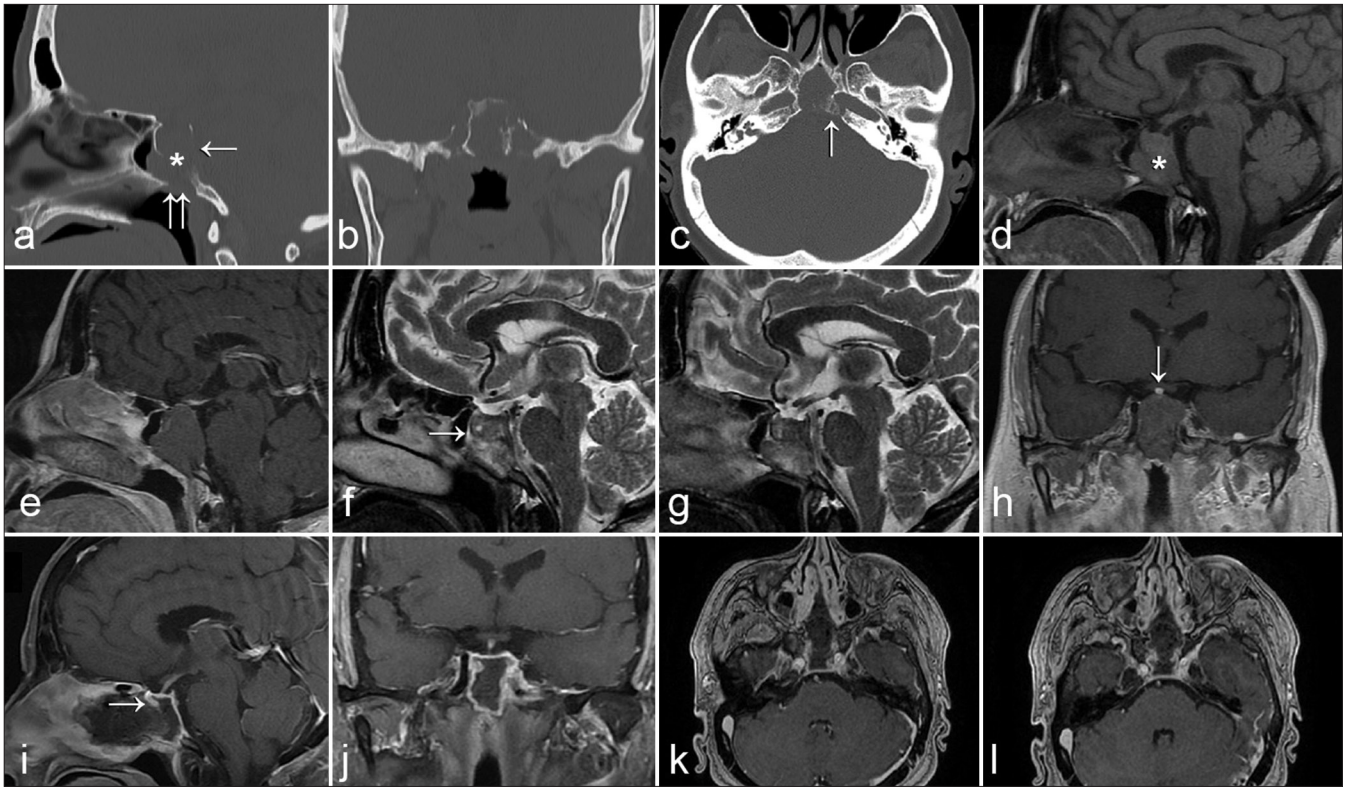

Figure 4: Neuroimaging findings in Case No. 2. (a-c) Preoperative computed tomography scans revealed extensive bone erosion, including the clivus (a single arrow), sellar floor (an asterisk), sphenoid sinus floor (a double arrows), and left petrous apex (c, arrow). (d-h) Preoperative magnetic resonance imaging (MRI) (d-h) revealed a T1-weighted isointense expansile lesion filling the sphenoid sinus cavity and the sella turcica (d, asterisk). The lesion was seen to have almost completely eroded and replaced the clivus. Very faint marginal enhancement is seen post-gadolinium injection. (e) No enhancement of the lesion was present. (f-g) On T2-weighted images, the lesion displayed mixed iso- and hyper-intense signals. Mucus within the remaining small cavity of the sphenoid sinus (f, arrow) and (h) compressed pituitary stalk (h, arrow) are observed. Postoperative contrast-enhanced (i) sagittal, (j) coronal, and (k-l) consecutive axial T1-weighted MRI demonstrated a gross total resection. The normal pituitary tissue is seen (i, arrow).

non-granulomatous FRS probably exist in this patient. It is important to note that non-invasive and invasive forms of FRS have been reported not to be distinct necessarily and may coexist in the same individual.[57] Clear evidence of histologic invasion in cases of AFRS [58,66] and foci of granulomatous inflammation in a patient with AFRS and orbital apex involvement [35] have previously been reported. Based on such findings, FRS was recommended to be considered a potentially progressive continuum, wherein a noninvasive disease may convert to or coexist with an invasive form.[57,66] An explanation for the questionable presence of fungal elements in our patient might be the findings of Cody *et al*., who proposed the term allergic fungal sinusitis-like syndrome to describe cases of rhinosinusitis in which histopathologic evidence of characteristic eosinophilic (allergic) mucin is present in the absence of fungal hyphae or cultures positive for fungi.[14]

The pathophysiological process of mucocele formation in cases of FRS is yet to be fully elucidated.[47] It is postulated, however, that the inflammatory process incited by the presence of fungal organisms leads to obstruction of the sinus ostia and retention of secretions, with subsequent expansion of the sinus walls. This mechanism seems to be the culprit in cases of FBs.[41,45,47,50] The accumulation of mucinous secretions over time may also be the underlying mechanism of mucocele formation in cases of AFRS. In AFRS, eosinophilic (allergic) mucin consisting of a mixture of eosinophils, mucus, Charcot–Leyden crystals, and fungal elements is produced and accumulates within the sinus, leading to demineralization of the sinus bony walls due to the release of inflammatory mediators and the pressure effect, ultimately causing expansion of the sinus and mucocele formation.[45] The high levels of prostaglandin E2 seem to be critical to the osteolytic process that contributes to the locally aggressive and expansile nature of these lesions.[13] Cystic degeneration of epithelial mucus glands or an inflammatory polyp has been alternatively proposed as a mechanism for mucocele formation.[23,38]

As it pertains to the microbiological profile in isolated sphenoid fungal mucocele cases, Aspergillus is by far the most common organism.[7,41] Other reported fungi include

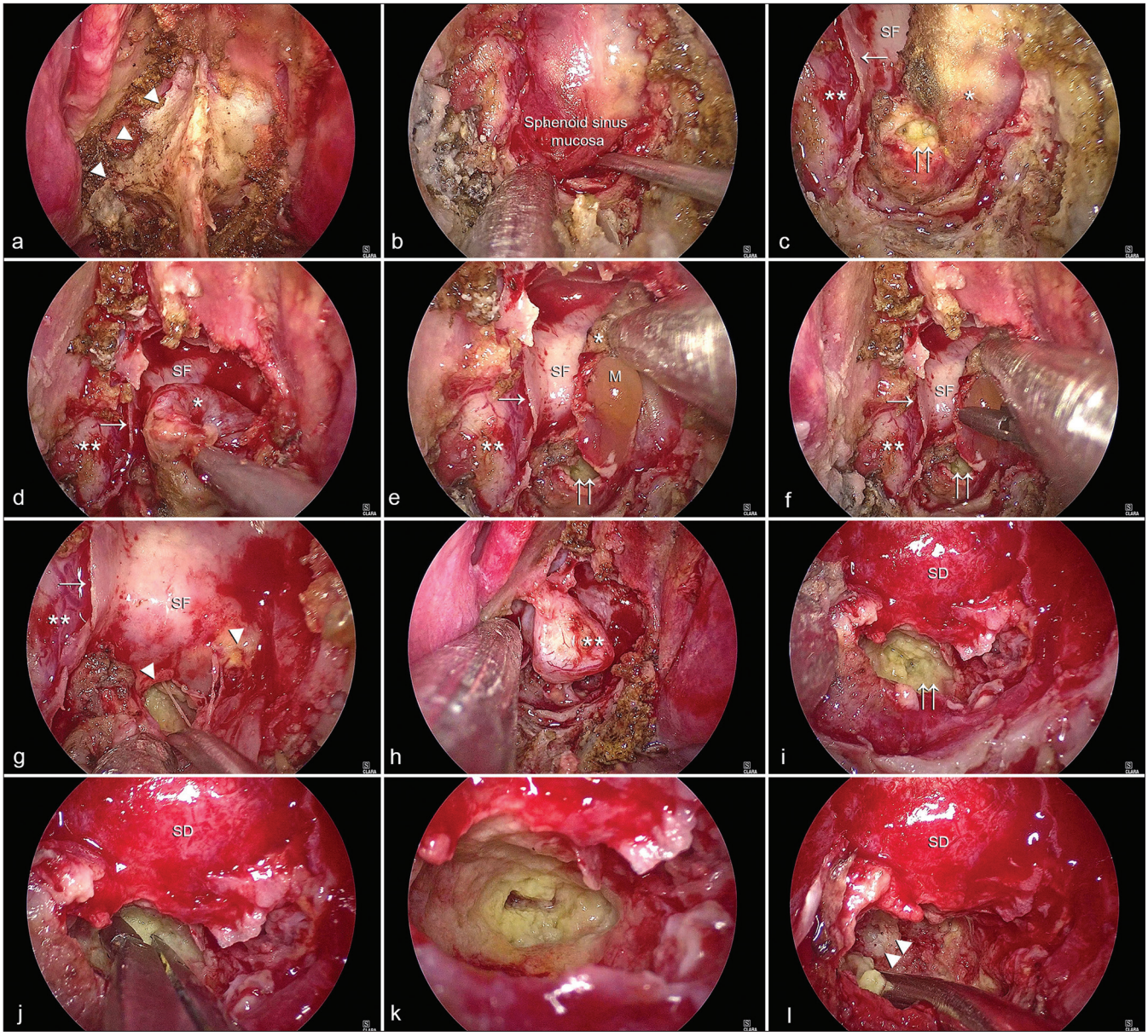

Figure 5: Step-wise intraoperative views during mucocele resection through an endoscopic endonasal transsphenoidal sphenoidectomy, Case No. 2. (a) Erosion of bone of the right side of the sphenoid face was noted at the beginning of the sphenoid phase of the procedure (a, arrowheads). (b) After wide sphenoidectomy, yellow discoloration of the sphenoid sinus mucosa was observed. In (c), the mucosa of the left half of the sinus (asterisk) was then coagulated and shrunk down where a clear view of the sphenoid septum (arrow), the bony sellar face (SF), and the mucosa of the right half of the sinus (double asterisks) was obtained. Yellow cheesy material (double arrows) is seen through a small rent in the left sphenoid mucosa. (d) Removal of the left sinus mucosal lining is performed. (e) Mucus content (M) is seen in (e) and (f) biopsied. (g) As the mucosal envelope of the left half of the sinus is completely removed, clear bone erosion and invasion of the sellar floor are observed (g, arrowheads). (h) The right sphenoid mucosa is then removed. In (i), the bony SF has been removed, the sellar dura is exposed, and intrasellar invasion is seen. (j) The invasive yellow material is biopsied, and (k) its superior extension within the sella is seen using a 45° endoscope in a close-up view. (l) As removal of the invasive material continues, bone erosion of the clivus and petrous apex (double arrowheads) is appreciated. Asterisk: Mucosa of the left half of the sphenoid sinus, Single arrow: Sphenoid septum, SF: bony sellar face, Double asterisks: Mucosa of the right half of the sphenoid sinus, Double arrows: Invasive cheesy content of the mucocele

Paecilomyces varioti,[67] *Paecilomyces lilacious*,[56] *P. boydii*,[72] *Alternaria*,[41] *Curvularia lunata*,[62] and *S. apiospermum*.[51] In concordance with the literature, in this series, *A. fumigatus* was isolated in 1 out of 3 cases for whom a fungal culture was performed. In the remaining cases, however, aspergillosis was diagnosed based on histopathological examination.

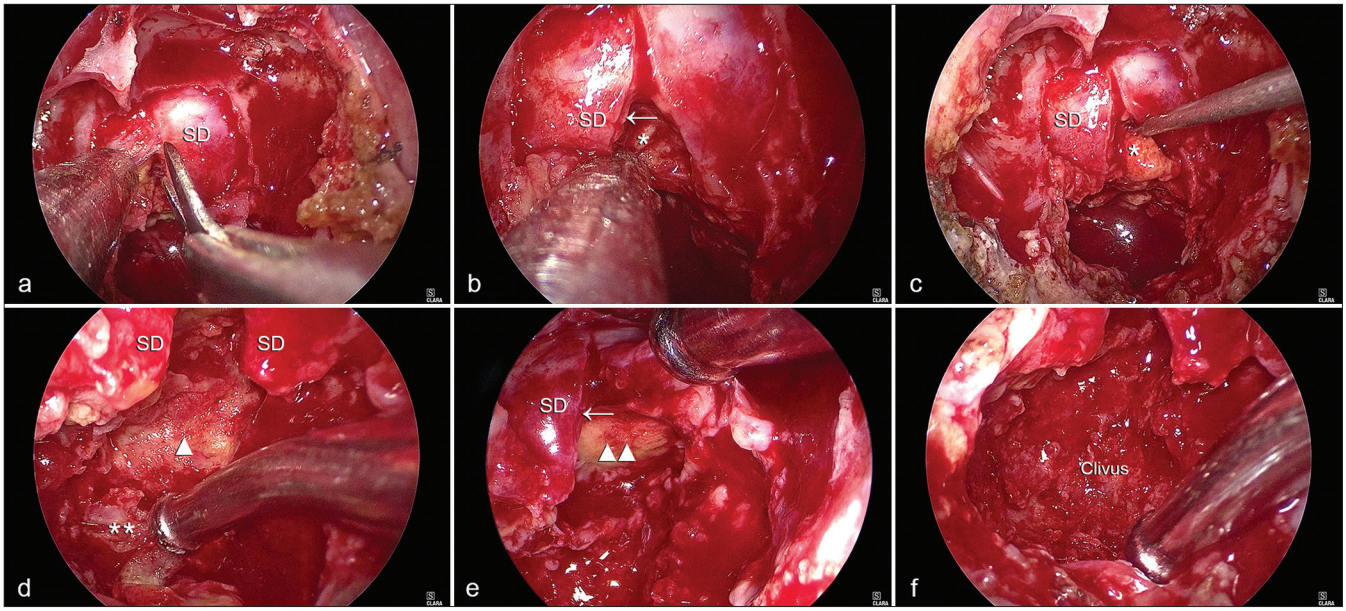

Figure 6: Intraoperative views during the intrasellar resection in Case No. 2. (a) Incision of the sellar dura is performed. (b) The normal pituitary (arrow) is seen compressed underneath the dura. The invasive material (asterisk) is seen filling the sellar cavity. (c) A pituitary ring curette is used to remove the invasive material (asterisk) from within the sella. (d) The yellow invasive material was adherent to the posterior wall of the sella (d, arrowhead) and (e) the descending cistern at the superior part of the sella, Arrow: SD (e, double arrows heads). Eroded petrous apex (d, double asterisks) is also observed. (f) A full view of the eroded clival bone within the clival recess is obtained. Single arrow: Pituitary gland, SD: Sellar dura.

Microbiological diagnosis of isolated sphenoid sinus fungal mucocele

In common practice, fungal cultures are frequently not obtained due to the large body of literature establishing fungi of *Aspergillus* species as the most common causative microorganisms of FRS.[7,32,34,40,41] In addition, the yield of fungal cultures in patients with AFRS is greatly variable and depends on the technique used [18], and fungal cultures are positive in only up to 50% of cases of FB.[20] In some of the reported cases, the correct diagnosis was only made after fungal cultures were performed. On histopathological examination, the causative agents were thought to represent Aspergillus most likely, but culture results were consistent with *C. lunata*,[47] *Alternata*,[41] and *Scedosporium*.[51] Nevertheless, fungal cultures should be correlated with the histopathological diagnosis of fungal elements. Precisely establishing the causative fungus type is clinically relevant for proper decisions related to the choice of antifungal agents and treatment durations.[51]

Treatment of isolated sphenoid sinus fungal mucoceles

The current consensus is to treat sphenoid sinus mucoceles surgically.[38,63,73] Asymptomatic mucoceles are, however, closely followed up, while symptomatic and rapidly growing mucoceles are operated upon.[11] In our opinion, even asymptomatic large mucoceles or those associated with bone remodeling or erosion are operative candidates. Urgent surgical decompression is indicated in cases of acute visual loss to preserve visual function.[38]

All patients in our series underwent endoscopic endonasal wide bilateral sphenoidectomy with marsupialization of the mucocele and clearance of its contents. Removal of the anterior and inferior walls of the sphenoid sinus is also undertaken. Many other groups have adopted this surgical philosophy, and it has now emerged as the standard treatment of choice.[34,38,40,47,51,73] In comparison to the transethmoidal approach, the midline paraseptal approach, which we perform in our cases, is, in our opinion, faster, anatomically more conservative and allows more panoramic visualization of the sphenoid sinus and the pathology therein.

As FBs are not invasive, systemic or topical antifungal therapy is not indicated.[17] In cases of AFRS, topical or oral steroid treatment has been recommended. The use of oral antifungals and immunotherapy is reserved for refractory cases.[17,24] In our series, all patients with AFRS were started on topical nasal steroids postoperatively. None of the patients received antifungal therapy except the patient with questionable invasive disease (Case No. 2). For patients with CN deficits, intravenous dexamethasone was started at the time of diagnosis and tapered down for 2 weeks after surgery. Endoscopic control was performed at 1 and 2 weeks after surgery, then at 6-month intervals during follow-up.

Limitations of the study

The limitations of our study include its retrospective nature, small number of patients, and unavailability of the specific causative fungus in the majority of patients. Larger scale prospective multicenter collaborative studies are clearly needed and should involve neurosurgeons, rhinologists, and infectious disease specialists.

CONCLUSION

Isolated sphenoid sinus fungal mucoceles are very rare and may be associated with serious and permanent neurological deficits. Advanced imaging studies provide appropriate clinical diagnosis. Histopathological and microbiological examination findings should both be obtained as they dictate the next steps of therapeutic intervention. Endoscopic endonasal wide sphenoidectomy is the surgical treatment of choice and should be performed in a timely manner to prevent permanent sequelae. A more widespread knowledge diffusion on this entity is required, and large-scale prospective multicenter collaborative studies are needed and should involve neurosurgeons, rhinologists, and infectious disease specialists.

Ethical approval

The Institutional Review Board approval is not required because the study is retrospective and all patient details were anonymized.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript, and no images were manipulated using AI.

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