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Original Article

The clinical features of endoscopic treated isolated sphenoid sinus diseases

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KEYWORDS

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Background: Isolated sphenoid sinus disease (ISSD) is a rare clinical entity with potentially serious complications. The etiological distribution of ISSD varies among different areas and ethnicities. We aimed to investigate the clinical features of patients with endoscopic treated ISSD. **Methods:** We retrospectively reviewed all patients with ISSD who had undergone endoscopic surgery between April 2013 and May 2019. The patient records were reviewed for demographic data, clinical presentations, endoscopic and imaging study findings, surgical outcomes and complications.

Results: A total of 37 patients with ISSD who underwent surgery were recruited. We divided patients into three groups according to etiology, including inflammatory diseases (78.4%), neoplasms (13.5%) and spontaneous cerebrospinal fluid (CSF) leaks (8.1%); fungal ball (62.2%) constituted the major cause of ISSD. Overall, the most common presenting symptom was headache or facial pain (65.5%). The endoscopic findings of bloody discharge and tumor lesions were mainly from the neoplasm group. Bony defects were more obvious on computed tomography in the neoplasm and CSF leak groups. Magnetic resonance imaging revealed a higher rate of involvement of the cavernous sinus (40.0%) and intracranial extensions (40.0%) in the neoplasm group. To summarize the surgical outcomes, the success rate was 97.1%, and the major complication rate was 5.4%.

Conclusion: ISSD represents a variety of etiologies, mostly comprising fungal ball in our area, while there is still a considerable proportion of ISSDs attributed to neoplasm and CSF leak. Untreated ISSD can result in serious complications. We recommend early surgical intervention for all patients with ISSD.

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Introduction

Isolated sphenoid sinus disease (ISSD) is a relatively rare clinical entity, accounting for 1.0–2.7% of all sinus diseases.¹ The presence of ISSD is easily neglected by patients or clinicians due to its nonspecific symptoms, deep anatomic location, and difficult accessibility for physical examination, leading to delayed diagnosis and treatment.^{1,2} However, with the growing use of computed tomography (CT) and magnetic resonance imaging (MRI), increasing numbers of ISSD have been diagnosed. ISSD may be found incidentally by neurosurgeons, neurologists, ophthalmologists, and oncologists.

Untreated sphenoid disease may result in serious complications such as blindness, diplopia, or life-threatening infection due to the proximity to critical structures, including the internal carotid arteries (ICAs), cavernous sinus, cranial nerves (CN) II, III, IV, V1, V2, VI, pituitary gland, and dura mater.³ In addition, a variety of etiologies have been reported for ISSD, including a notably high incidence of neoplasms (13.4–18.4%), in the literature.^{4,5} The range of malignant pathologies includes squamous cell carcinomas, salivary gland carcinomas, malignant soft tissue tumors, lymphomas, plasmacytomas, and metastatic lesions.^{4,5} Given the serious complications and the high rate of neoplasms, all patients with ISSD are recommended as surgical candidates warranting early intervention.^{4–6}

Endoscopic sphenoidotomy can be safely and effectively performed through several approaches, including transethmoidal, transnasal, transseptal, and transethmoidal–pterygoidal approaches.⁸ We have chosen the transethmoidal approach as our principal surgical modality for ISSD given its superior intraoperative flexibility and maneuverability, its wide lateral visualization, and the numerous reliable anatomic landmarks in the posterior sphenoid sinus, which allows us to avoid iatrogenic catastrophic complications such as blindness, cerebrospinal fluid (CSF) leakage, or massive hemorrhage from ICAs; as a result, the transethmoidal approach has been called the “default” approach for sphenoid sinus surgery.⁷

In this study, we reviewed the clinical symptoms, duration of delayed diagnosis, diagnostic tools, and pathoetiologies of ISSD to address its indications, surgical outcomes and complications to clarify the clinical features and management of ISSD in Taiwan.

Material and methods

Patients

We retrospectively reviewed consecutive patients who underwent endoscopic sinus surgery (ESS) at the Department of Otolaryngology of National Taiwan University Hospital, a tertiary referral center, between April 2013 and May 2019. This retrospective study was conducted under approval from the Institutional Review Board of National Taiwan University Hospital.

Patients who had isolated sphenoid sinus disease on CT images were enrolled in our study, and those patients who had sphenoid disease with concomitant involvement of the remaining paranasal sinuses or previously underwent sinus/

skull base surgery were excluded from our study. The study population underwent endoscopic transethmoidal sphenoidotomy, performed by the same surgeon, for the purposes of surgical treatment or diagnostic biopsy. The medical records were reviewed for demographic data, clinical presentations, and preoperative rhinoscopic findings. The duration from symptomatic onset to confirmed diagnosis was recorded, and patients not presenting with symptoms of sinusitis but diagnosed based on imaging studies were identified as asymptomatic patients. Each patient underwent a CT study for diagnosis and intraoperative navigation, and MRI studies were performed preoperatively in patients with cranial nerve deficits or other symptoms of intracranial manifestations.

The surgical pathologies were mainly classified into three categories: inflammatory diseases, neoplasms and CSF leaks. With regard to surgical outcomes, assessment of the success rate of surgery was established based on the resolution of symptoms and improvements in endoscopic findings or radiologic imaging. Early and late complications, morbidity, and mortality were also reviewed. Major surgical complications were defined as neurologic sequelae (e.g., visual disturbance, diplopia), massive bleeding, or life-threatening infectious conditions (e.g., septic shock, meningitis, cavernous sinus thrombosis).

Surgical procedures for transethmoidal sphenoidotomy

We applied standard transethmoidal sphenoidotomy techniques for isolated sphenoid sinus diseases. After general anesthesia and navigation system setup, cotton pledgets, soaked in 2% lidocaine and epinephrine, were inserted towards the olfactory cleft and the sphenoid ethmoidal recess for mucosal decongestion. The middle turbinate and mucosa around the sphenopalatine foramen were injected with 1% lidocaine with epinephrine 1:100,000. Part of the perpendicular portion of the middle turbinate was resected for better visualization of the superior turbinate and to provide a corridor for sphenoidotomy. The bulla ethmoidalis was left intact due to spared anterior ethmoid sinus disease. The lower third of the superior turbinate was trimmed, and partial posterior ethmoidectomy was performed as needed. Then, the natural ostium of the sphenoid sinus could be easily identified. The extent of enlarging sphenoid sinus ostium depended on the etiology of the sphenoid sinus disease. When the sphenoid sinus ostium was open in inflammatory disease, attempts were made to avoid circumferential injury of the ostium to prevent postoperative stricture of the opening. For cases of tumor and CSF leak, the anterior wall was removed as much as we needed to expose the sphenoid sinus widely enough for tumor removal and skull base reconstruction.

Statistics

Data analyses were performed using SPSS for Mac, version 23. Data are expressed as the mean values (with SD values), and all statistical tests were two-tailed. Nonparametric tests were applied to the data, and the Kruskal–Wallis test was used to identify differences among groups. P values of

0.05 or less were considered to indicate statistical significance.

Results

In total, 37 patients with ISSD who underwent endoscopic surgery were recruited for our study. The patients' characteristics and symptoms are summarized in Table 1. There were 11 males and 26 females, with a female preponderance in a 1:2.4 ratio. The patients were divided into three categories based on pathologies, including inflammatory diseases, neoplasms and CSF leaks. The patients in the inflammatory disease group were significantly older than those in the other two groups. Among all ISSD patients, the most common symptom was headache in 23 patients (62.2%), followed by thick nasal discharge in 21 patients (56.8%), nasal congestion in 14 patients (37.8%), and blood-tinged sputum in 7 patients (18.9%). In addition, it is important to note that five patients (13.5%) presented with cranial nerve neuropathies (CNNs), such as visual disturbance in 2 patients (5.4%), diplopia due to oculomotor nerve palsy or abducens palsy in 4 patients (10.8%), and

trigeminal neuralgia in one patient (2.7%). Moreover, three patients (8%) with suspected CSF rhinorrhea presented with a gushing of clear fluid in the rhinorrhea, worsened by changes in position and straining. Interestingly, four asymptomatic cases (10.8%), consisting of three cases of fungal ball and one case of invasive pituitary adenoma, were unanticipatedly discovered on radiologic imaging during a workup for other reasons. The duration of delayed diagnosis was 24.2 ± 30.8 (mean \pm SD) months, with a range of 0.5–120 months.

Of the 29 patients in the inflammatory disease group, 23 patients had fungal balls, four had chronic rhinosinusitis without nasal polyps (CRSsNP), one had chronic rhinosinusitis with nasal polyps (CRSwNP), and one had mucocele. The five patients in the neoplastic group consisted of two with inverted papillomas, one with seromucinous hamartoma, one with squamous cell carcinoma, and one with invasive pituitary adenoma. Finally, among the three patients in the CSF leak group, two had meningocele and one had encephalomeningocele (Table 2). The overall preoperative nasal endoscopic findings were thick discharge in 12 patients (33.3%), blood-tinged discharge in six (16.7%), tumors or polyps in four

Table 1 Patients' characteristics of isolated sphenoid sinus diseases.^{a,b}

	Patient Group, number			Total (n = 37)
	Inflammatory Diseases (n = 29)	Neoplasms (n = 5)	Cerebrospinal Fluid Leaks (n = 3)	
Age, mean \pm SD (year)	63.2 \pm 10.7**	46.4 \pm 15.9**	43.3 \pm 4.2**	59.3 \pm 13.2
Age range (year)	41–82	33–72	40–48	33–82
Sex				
Male	8 (27.6)	2 (40.0)	1 (33.3)	11 (29.7)
Female	21 (72.4)	3 (60.0)	2 (66.7)	26 (70.3)
Smoking	2 (6.9)	1 (20.0)	1 (33.3)	4 (10.8)
Concomitant diseases				
Atopic disease	5 (17.2)	1 (20.0)	0	6 (16.2)
Diabetes mellitus	4 (13.8)	0	0	4 (10.8)
Hypertension	10 (34.5)	0	2 (66.7)	12 (32.4)
Cardiac disease	5 (17.2)	0	0	5 (13.5)
Pulmonary disease	2 (6.9)	0	0	2 (5.4)
Malignancy	4 (13.8)	0	0	4 (10.8)
Physical symptoms				
Headache or facial pain	19 (65.5)	2 (40.0)	2 (66.7)	23 (62.2)
Thick nasal discharge	19 (65.5)	2 (40.0)	0	21 (56.8)
Nasal congestion	10 (34.5)	4 (80.0)	0	14 (37.8)
Hyposmia or anosmia	2 (6.9)	0	0	2 (5.4)
Fever	1 (3.4)**	0**	2 (66.7)**	3 (8.1)
Bloody-tinged sputum	4 (13.8)*	3 (60.0)*	0*	7 (18.9)
Cough	5 (17.2)	1 (20.0)	0	6 (16.2)
Neurological symptoms				
Blurred vision	2 (6.9)	0	0	2 (5.4)
Diplopia	3 (10.3)	1 (20.0)	0	4 (10.8)
Neuralgia	1 (3.4)	0	0	1 (2.7)
No symptom	3 (10.3)	1 (20.0)	0	4 (10.8)
Duration of symptoms onset to diagnosis (months)	28.6 \pm 33.3	5.1 \pm 4.7	11.0 \pm 6.6	24.2 \pm 30.8

^a Data were presented as mean \pm SD or number (%).

^b Comparison among groups using Kruskal–Wallis Test.

* $P < 0.05$, ** $P < 0.01$.

(11.1%), and clear rhinorrhea with suspected CSF leak in two (5.6%). Endoscopic examinations revealed a higher proportion of blood-tinged discharge (60%) and tumor or polyp-like lesions (60%) in the neoplastic group. Endoscopic findings of clear discharge (66.7%) were highly suggestive of CSF leaks ($p < 0.001$).

A preoperative CT scan was performed for all patients. Overall, the most frequent findings were sclerotic bony margin (27/37, 73.0%) and heterogeneous calcified density of sinus content (19/37, 51.4%). These two features were identified more often in the inflammation group. Bone remodeling was noticed more often in the neoplasm group due to the mass effect. We observed more bony defects in the neoplasm group and the CSF leak group ($p < 0.05$) (Table 2). We also summarized the representative CT and MR images of each of the three groups, as shown in Figs. 1–3. Bony defect on the preoperative CT images could be a warning sign that one case of non-invasive fungal ball presented with diplopia (Fig. 1a,b), and another case of acute sphenoid sinusitis developed septic shock after surgery (Fig. 1c,d). MRI studies were performed in 16 patients,

as they presented with (1) clinical manifestations of CNs or intracranial infections, (2) intractable unexplained headache requiring imaging diagnosis by neurologists, (3) suspected CSF rhinorrhea, and (4) suspected neoplasms or inflammatory lesions with bony defects over the sphenoid sinus wall or suspected intracranial extension on CT scan. We observed an expansile tumor invading the skull base in one case of squamous cell carcinoma (Fig. 2 d-f). For cases of CSF leak, we could see skull base defects on the CT images, and the MRI could identify the meningocele easily (Fig. 3 a-c).

Regarding surgical outcomes, the mean duration of follow-up was 17.7 ± 22.0 (mean \pm SD) months, with a range of 0.5–79 months. Two cases, including one sinonasal carcinoma and one invasive pituitary adenoma, were excluded from these statistics because the patients only underwent tissue biopsy and would need further radiation therapy. The overall success rate of surgery was 97.1%, corresponding to 34 of 35 patients who attained subjective and objective improvement after ESS. As we could see in Fig. 2 a-c, one case of inverted

Table 2 Endoscopic findings, imaging findings, and post-operative course.

	Patient Group, number			Total (n = 37)
	Inflammatory Diseases (n = 29)	Neoplasms (n = 5)	Cerebrospinal Fluid Leaks (n = 3)	
Etiology (number)	Fungal ball (23) CRSsNP (4) CRSwNP (1) Mucocele (1)	Intervent papilloma (2) Seromucinous harmatoma (1) Sinonasal carginoma (1) Pituitary adenoma (1)	Meningocele (2) Encephalomeningocle (1)	
Endoscopic findings ^{a,b}				
Thick discharge	11 (37.9)	2 (40.0)	0	13 (35.1)
Blood-tinged discharge	3 (10.3)*	3 (60.0)*	0*	6 (16.2)
Clear discharge	0 [†]	0 [†]	2 (66.7) [†]	2 (5.4)
Tumor or polyp	1 (3.4)**	3 (60.0)**	0**	4 (10.8)
CT images ^{a,b}				
Bony margins:				
Normal	1 (3.4)	1 (20.0)	0	2 (5.4)
Sclerosis	25 (86.2)**	2 (40.0)**	0**	27 (73.0)
Remodeling	3 (10.3)*	3 (60.0)*	0*	6 (16.2)
Defect	6 (20.7)*	3 (60.0)*	3 (100.0)*	12 (32.4)
Content of opacification				
Partial opacification	13 (44.8)	2 (40.0)	3 (100.0)	18 (48.6)
Complete opacification	16 (55.2)	3 (60.0)	0	19 (51.4)
Heterogenous calcified density	18 (62.1)*	1 (20.0)*	0*	19 (51.4)
MR images ^{a,b}				
Cases receiving MRI studies	10 (27.0)	3 (60.0)	3 (100.0)	16 (43.2)
Involvement of cavernous sinus	1 (3.4)*	2 (40.0)*	0*	3 (8.1)
Intracranial extension	0**	2 (40.0)**	0**	2 (5.4)
Complications (number) ^{a,b}	Septic shock (1)	0	Temporal abscess (1)	2 (5.4)
Mean follow-up time months) ^{a,b}	13.4 \pm 17.8	32.4 \pm 34.8	34.7 \pm 24.7	17.7 \pm 22.0
Recurrence ^{a,b}	1 (3.4)	0	0	1 (2.7)

^a Data were presented as mean \pm SD or number (%).

^b Comparison among groups using Kruskal–Wallis Test.

* $P < 0.05$, ** $P < 0.01$, [†] $P < 0.001$.

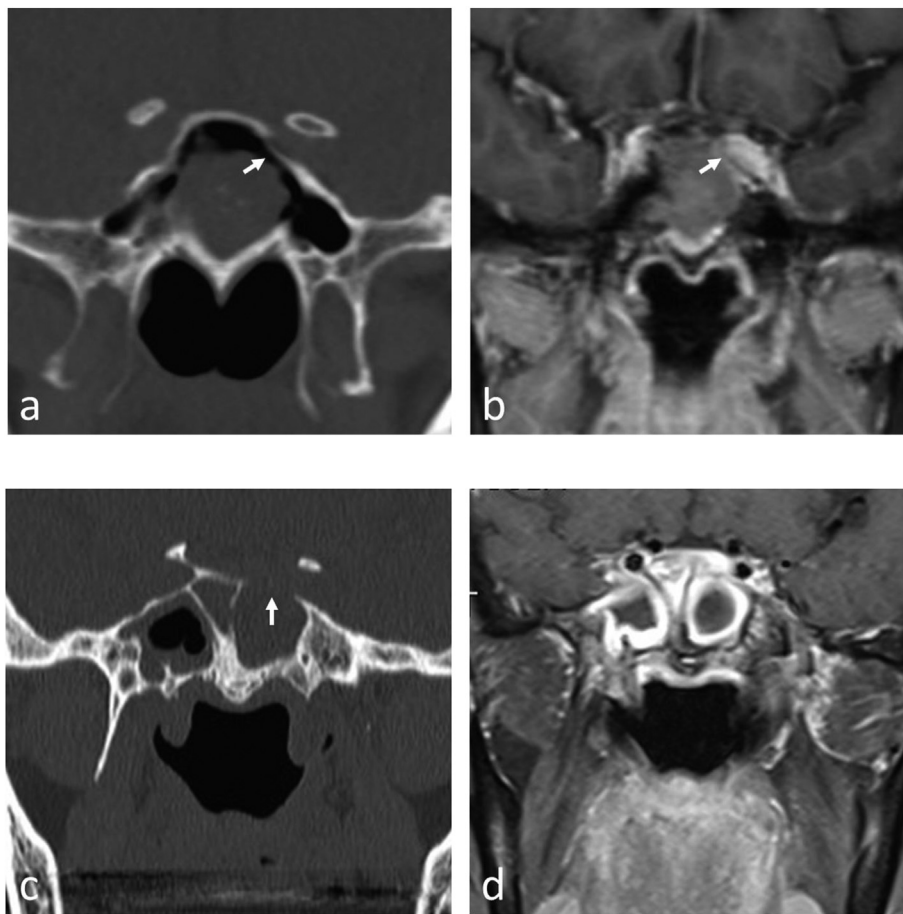


Figure 1 Inflammatory isolated sphenoid sinus diseases. (a)–(b) A case of *Aspergillus* fungal ball and inflammatory polyps on pathology, presented with diplopia attributed to left abducens palsy. (a) Noncontrast CT scan shows a heterogeneous calcified opacification in the left sphenoid sinus and a small bone defect (arrow) identified in the left sinus wall; (b) on MRI, postcontrast T1WI shows increased intracranial infiltration below the anterior clinoid process (arrow). (c)–(d) A case of sphenoiditis complicated with postoperative septic shock. (c) Noncontrast CT scan shows a complete homogenous opacification in the left sphenoid sinus with a bone defect in the left sinus roof (arrow) and focal erosion at the sphenoid septum (arrowhead); (d) on MRI, post-contrast T1WI shows peripheral mucosal enhancement and hypointense fluid content.

papilloma was completely removed, and there was no recurrence in post-operative 15 months. The major surgical complication rate was 5.4%, including one patient with CRSsNP developing septic shock and one with spontaneous CSF leak complicated with temporal lobe abscess (Fig. 3 d-f).

Discussion

ISSD is a relatively rare clinical entity that represents a variety of etiologies with potentially serious complications. It has been reported that the majority are inflammatory diseases (61.1–86.9%).^{4,5,8,9} Nevertheless, a considerable proportion of ISSDs are attributed to neoplasm (13.4–18.4%) and spontaneous CSF leak (7.7–10.9%).^{4,5} The main pathophysiology of chronic rhinosinusitis basically originates from the ostiomeatal complex with involvement of more than one of the related sinuses; therefore, inflammation confined to an isolated sphenoid sinus is less common.^{4–6,8–11} In a systematic review, chronic

rhinosinusitis without nasal polyps (28.3%) and mucocele (20.3%) were the most common etiologies in the inflammatory group, while fungal sinusitis accounted for a lower proportion (12.5%).⁵ However, in our area, the pathological result was remarkably different from that in previous literature. Fungal balls constituted the majority of cases (62%) of ISSD. Lim *et al* reviewed a case series of isolated sphenoid sinus fungal balls from the past 20 years, and they found a growing number of diagnosed cases. The mean age of the patients was 63.1 years, and there was a significant female predominance.¹² We also observed older ages (mean age of 64.2 years) and a significant female preponderance in a 1:2.8 ratio (male to female) in our cases, and 13% of patients complicated with CNNs warranted surgical intervention. Fungal sinusitis could be effectively managed with ESS by removal of the fungal concretions, and near perfect outcomes were reported (success rate of 99% by Kim *et al*¹³; success rate of 100% in our study). Some may argue that ISSD may be only one facet of the common sinonasal disease. Thus, we also collected consecutive cases undergoing endoscopic sinus surgery in the same

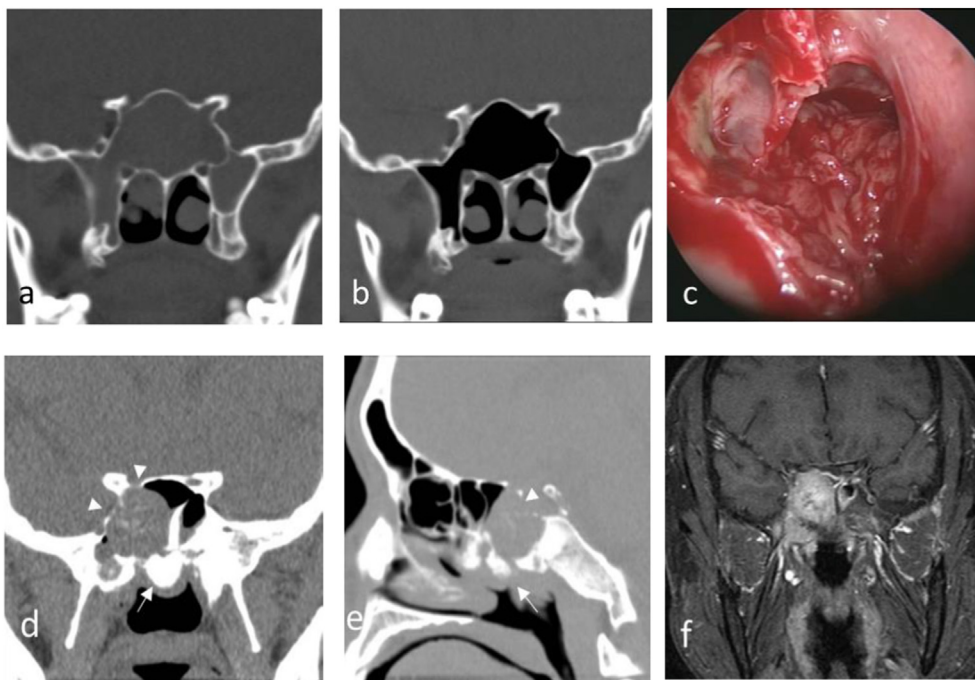


Figure 2 Neoplastic isolated sphenoid sinus disease. (a)–(c) A case of inverted papilloma. (a) Pre-OP noncontrast CT scan reveals a homogenous expansile soft tissue density in the bilateral sphenoid sinuses; (b) post-OP CT scan 15 months after ESS shows that the patient was completely cured from the disease; (c) an intraoperative endoscopic view shows inverted papilloma in sphenoid sinus. (d)–(f) A case of sinonasal carcinoma in the right sphenoid sinus. (d), (e) Noncontrast CT scan reveals heterogeneous opacification containing calcified densities, which was misinterpreted as fungal ball. Bone defects are found in the lateral wall and sellar floor of the right sphenoid sinus (*arrowhead*); some osteosclerotic changes are noted at the posterior nasal septum and sphenoid septum (*arrow*); (f) on MRI, postcontrast T1WI shows a heterogeneous enhancing mass with invasion of the right inferior portion of the sella turcica and right cavernous sinus.

study period, and there were 439 non-ISSD patients, including 400 patients with inflammatory diseases and 39 patients with neoplasms. Among the patients with inflammatory diseases, 217 patients had CRSwNP, 114 patients had CRSsNP, 66 patients had fungal sinusitis, and 3 patients had mucocele (*Supplement Figs. 1 and 2*). Evidently, ISSD remains a special entity among sinonasal diseases. Of 66 non-ISSD patients with fungal sinusitis, 61 patients had fungal balls in the unilateral maxillary sinus, one patient had fungal balls in the bilateral maxillary sinuses, one patient had fungal balls in both the maxillary sinus and sphenoid sinus, two patients had fungal balls in the unilateral posterior ethmoid sinus, and one patient had fungal balls in the ipsilateral posterior ethmoid and sphenoid sinus. The unilateral maxillary sinus is still the most common involvement site, and the unilateral sphenoid sinus is the second most commonly involved sinus. No fungal balls were found in the frontal or anterior ethmoid sinuses in our case series.

The diagnosis of ISSD is based on clinical symptoms, endoscopic evaluation, and radiologic imaging. In our study, 10.8% of patients with chronic disease were asymptomatic at diagnosis. The difficulty in early diagnosis of ISSD may arise from the vagueness of the symptoms, an insidious clinical course, and low sensitivity in nasal endoscopic evaluation.^{9,10,14} From our retrospective review, the most common symptom was headache (62.2%), which may be aggravated by head movement, and the location of

headache was nonspecific, as it could be found in the occipital, vertex, frontal, temporoparietal, periorbital, retro-orbital, or midfacial areas, which is similar to the results reported in the literature.^{7,9,15,16} After headache, the most common symptoms were purulent rhinorrhea/post-nasal dripping (57%) and nasal congestion (38%); however, these nasal symptoms might be regarded as nonspecific, requiring further imaging studies to evaluate the sphenoid sinuses. Therefore, it is not surprising that the time of the diagnosis of ISSD had a significant delay of 24.2 months from the onset of symptoms. A systematic review indicated a pooled CNN rate of 16.3%, which is similar to the results from our data (14%).⁵ CNNs are presumed to be mainly produced by the compressive effect from the expanding lesion in the sphenoid sinus, regardless of the etiology, (even those with a benign nature); the outward pressure compresses the neighboring cranial nerves, thereby resulting in visual disturbance (5%), diplopia (11%), and trigeminal neuralgia (3%) in our cases. The study from Lee *et al* supports surgical treatment for ISSD with visual disturbances or diplopia attributed to compressive optic neuropathy, abducens palsy, or oculomotor nerve palsy.¹⁶ Furthermore, Kim *et al* reported a 100% improvement in visual disturbances for patients in the inflammatory group in ISSD.⁸ All of our cases, with the exception of one case of sinonasal carcinoma, had complete recovery from the symptoms of CNNs after surgical intervention, which is thought to be indirect evidence indicating that CNNs are related to compressive effects.

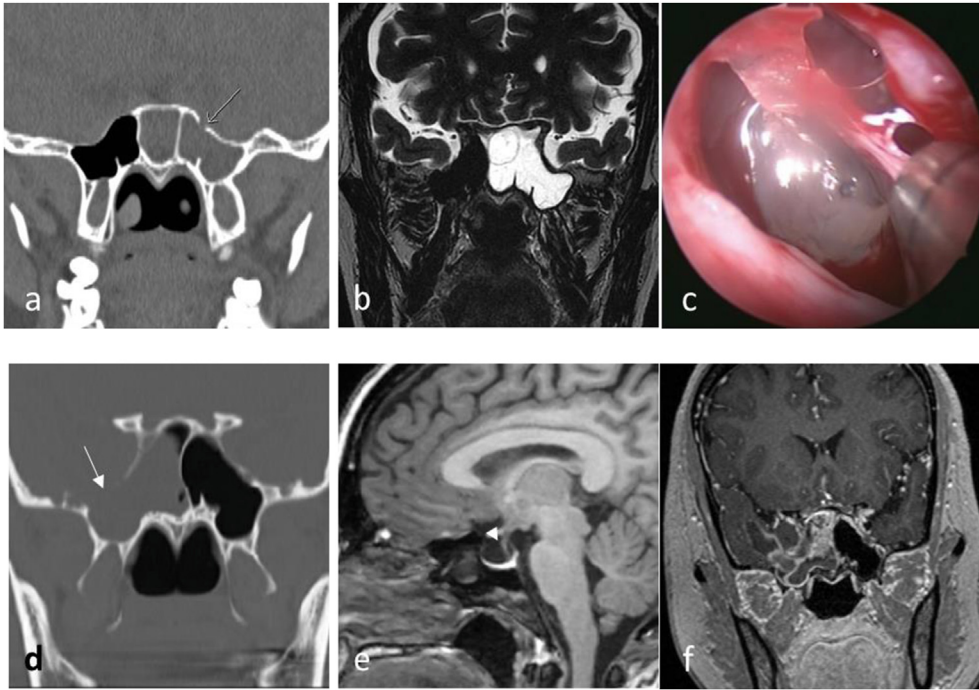


Figure 3 Spontaneous CSF leak (a)–(c) A case of spontaneous CSF leak. (a) Pre-OP noncontrast CT scan reveals a homogenous opacity in the left sphenoid sinus with a tiny bone defect in the sinus roof (*arrow*); (b) T2WI MR cisternography shows a CSF-filled meningocele in the left sphenoid sinus; (c) an intraoperatively endoscopic view shows a meningocele in the left sphenoid sinus with active CSF leak. (d)–(f) Another case of spontaneous CSF leak suffering from temporal abscess after surgery. (d) Similar to the previous case, a preoperative CT scan shows a homogenous opacification but with a remarkable bone defect in the roof of the lateral recess of the right sphenoid sinus (*arrow*); (e) on MRI, an empty sella with an infundibulum sign (*arrowhead*) is also identified on postcontrast T1WI; (f) 10 days after surgery, postcontrast T1WI reveals a rim-enhancing abscess with perifocal edema at the right temporal lobe, with connection to the right sphenoid sinus.

Sinonasal endoscopy helps determine a diagnosis of ISSD when positive local findings are visualized at the sphenoidal recess, but the absence of discharge from the sphenoid ostium cannot exclude a diagnosis attributed to a relatively low detection rate. From our data, only 49% of cases were detected with positive findings from nasal endoscopy, and the most frequent positive finding was thick discharge (33%) produced by fungal balls and CRSsNP. It is not surprising that the endoscopic finding of tumors or polyps were mainly identified in the CRSwNP and neoplastic groups, whereas bloody tinged discharge could be observed in patients with malignant tumors or fungal balls. CSF rhinorrhea should be suspected when a continuous clear discharge is observed within the sphenoidal recess on examination and can be particularly proved by glucose strip test or β 2-transferrin.

Radiologic imaging, such as CT or MRI, can work in concert to obtain the diagnosis by delineating bony changes, the nature of lesions, and the extent of intracranial invasion. Preoperative CT features reveal changes in both the contents of opacification and bony margins. The changes in the contents of opacification range from mucosal thickening, partial opacification, or complete opacification and identify whether heterogenous calcified densities are present.¹⁷ In the current study, the proportion of partial opacification was nearly equal to that of complete opacification among the categorized groups, and therefore,

the application of the degree of opacification in discriminating among the spectrum of pathologies is limited. Approximately half of the overall cohort presented with heterogeneous calcified densities (51%, 19 cases), while histopathologically, they were almost exclusively related to the presence of fungal balls (i.e. 18 of 19 cases); one case of sinonasal carcinoma was not associated with this condition. Therefore, ISSDs presenting with signs of heterogeneous calcified density on CT scan strongly indicate a diagnosis of fungal sinusitis, but we should also be open to the possibility of malignancy. The CT scan is especially valuable in the evaluation of bony changes with sufficient detail to differentiate the spectrum of pathology. In our data, 95% of patients had changes in the bony margins that mostly comprised bone sclerosis (73%). Focal bone sclerosis or hyperostosis involving the sinus wall is believed to be related to chronic osteitic bony changes by prolonged mucoperiosteal reactions, such as CRS and fungal sinusitis, or the tumor origin of neoplasms, such as inverted papilloma.^{17–19} From the literature, sphenoid sinus bone defects on CT scans are characteristic of neoplasms and even malignancies, including primary tumors in the sphenoid sinus, secondary lesions extending from neighboring structures (i.e., pituitary glands, meninges, clivus, etc.), and metastasis from other sites. Otherwise, invasive fungal sinusitis, CSF leakage, meningocele, meningoencephalocele, and sometimes mucocele might generate localized bone

defects or destruction on CT scans.¹⁷ Under these circumstances, MRI is more sensitive (100%) than CT scan (80%) not only in distinguishing soft tissue tumors from other types of disease but also in accurately delineating the extent of tumors with or without intracranial extension.^{17,19}

Spontaneous CSF leakage in the sphenoid sinus is a rare clinical entity. Only ten percent of all CSF leaks originate from the sphenoid sinus, of which 7% are attributed to a spontaneous (or idiopathic) etiology.²⁰ Growing evidence supports increased intracranial pressure (ICP) and skull base defects occurring during embryologic development as the main causes of spontaneous CSF leak.^{20,21} Empty sella syndrome has been broadly regarded as an indirect sign of increased ICP; additionally, patients suffering from spontaneous CSF leak or idiopathic intracranial hypertension are often young or middle-age obese women.^{22–24} Additionally, the lateral recess of the sphenoid sinus is one of the most frequent locations of skull base defects for spontaneous CSF leak due to an attenuated lateral recess roof in a well-pneumatized sphenoid sinus and the development of arachnoid pits from the underlying increased ICP; moreover, surgical repair is currently the only treatment for spontaneous CSF leak in this area since no self-healing has ever been reported merely by conservative management.^{25,26} The surgical repair of CSF leak defects is challenging; a high failure rate from the initial repair has been reported, and subsequent CSF leaks requiring re-exploration are not uncommon. Transsphenoidal endoscopic techniques have become the gold standard for the repair of CSF leaks owing to their minimal invasiveness and favorable success rates higher than 90% and have gradually replaced the open craniotomy approach.^{20,27} With the aid of CT or MR cisternography, transsphenoidal endoscopy can help us precisely localize CSF leak defects, dictate the endoscopic approaches, and further increase the success rate of surgical closure.

Although some patients with isolated sphenoiditis could be treated with medical therapy alone, Gilony *et al* reported a relatively high morbidity (8.3% developing life-threatening complications) and mortality (2.9%) in isolated sphenoiditis patients, especially among immunocompromised patients.⁶ In the current study, all patients with isolated sphenoiditis referred for surgical treatment had already received maximal initial medical treatment, consisting of high-dose broad-spectrum antibiotics, topical steroids, and nasal douching, but the symptoms still persisted or had even deteriorated with complications. We suggest early surgical intervention for drainage of isolated sphenoiditis, especially for patients who have symptoms that do not fully respond to maximal medical treatment or present with more aggressive clinical conditions, such as sepsis, meningitis, cavernous sinus thrombosis, and neurological or ocular symptoms. The most common surgical approaches for ISSD noted by Moss were transtethmoidal, transnasal, and transseptal, with a pooled symptomatic improvement rate of 91.8% and surgical complication rate of 1.5%.⁵ The selection of the optimal approach for ISSD is dependent on the sphenoid pathology, the degree of pneumatization of the sphenoid sinus, and the extent of exposure of the lesion required. If the lesion presents near the midline or a histopathologically suspected pituitary adenoma, transseptal or transnasal approaches are usually

sufficient for management; however, if the lesion extends far laterally into the well-pneumatized lateral recess of the sphenoid sinus, the transtethmoidal–pterygoidal approach can result in the most lateral exposure of the lesion.⁷

In conclusion, ISSD is a rare clinical entity but represents a variety of pathoetiologies, mostly comprising fungal balls in our area; nevertheless, a considerable proportion of ISSD was attributed to neoplasms and spontaneous CSF leaks. The most frequent symptom was headache, whereas some cases were asymptomatic on diagnosis. The vagueness of symptoms, an insidious clinical course, and low sensitivity in the endoscopic evaluation of ISSD contributed to significant delays in diagnosis. Untreated ISSD can result in serious complications such as sepsis, meningitis, or CNNs due to the proximity of critical structures. Endoscopic transtethmoidal sphenoidotomy is a safe and effective approach in the management of ISSD, with a 97.1% success rate and a 5.4% major complication rate. We recommend early surgical intervention for all patients with ISSD.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jfma.2020.11.005>.

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