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CLINICAL ARTICLE - NEUROSURGICAL TECHNIQUES

Sphenoid sinus aspergilloma in trans-sphenoidal surgery for pituitary adenomas

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Abstract
Background Simultaneous appearance of sphenoid sinus aspergilloma and pituitary adenoma is a very rare finding.
Methods Retrospective analysis of patients with sellar and sphenoid sinus mass lesions who underwent trans-sphenoidal surgery was performed. Demographic data, medical history, predisposing factors, clinical picture, neurological status and radiological findings were reviewed. All patients underwent a trans-sphenoidal microsurgical treatment, and acquired specimens underwent both histopathological and microbiological analysis.
Results Sphenoid sinus aspergilloma was encountered in seven patients. Three patients had an isolated sphenoid sinus aspergilloma and four patients with pituitary macroadenoma had a sphenoid aspergilloma as an incidental finding.
Conclusions Sphenoid sinus aspergilloma can be found during trans-sphenoidal surgery for pituitary adenomas. Sphenoid sinus extirpation followed by adenomectomy is the treatment of choice unless invasive aspergilloma is encountered requiring additional antifungal therapy.

Keywords Aspergilloma · Sphenoid sinus · Pituitary adenoma · Trans-sphenoidal surgery · Treatment

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Introduction

Isolated aspergilloma of the sphenoid sinus, although rare, is well documented [1, 16, 19, 27].

Sphenoid aspergillomas are known to mimic pituitary adenomas especially when associated with an atypical presentation, previous history of sellar surgery and appearance in immunocompetent patients [2, 13].

Simultaneous appearance of sphenoid sinus aspergilloma and pituitary adenoma is extremely rare.

Five previous reports of sellar aspergillosis had been reported, most of them in the form of pituitary abscesses [10, 17, 18, 27, 28]. Those were not associated with a pituitary tumour. Furtado et al. [13], Azarpira et al. [3], Birdenstine et al. [8] and Ahmeti et al. [1] have each reported a case of a sphenoid sinus aspergilloma associated with a pituitary adenoma.

We report a small series of seven patients, which included three patients with an isolated sphenoid sinus aspergilloma and four patients with a simultaneous appearance of sphenoid sinus aspergilloma and pituitary adenoma.

Methods and materials

A retrospective analysis of more than a thousand patients with sellar and sphenoid sinus lesions who underwent trans-sphenoidal surgery at the Department of Neurosurgery, Sestre milosrdnice University Hospital Centre, Zagreb, Croatia in a period from 2002 to 2012 was performed. Only mass lesions in the sphenoid sinus and sellar region with pathologically proven fungal involvement were included. Intracerebral fungal lesions and abscesses were excluded from the study. Informed patient consent for all surgically treated patients was obtained.

Thirteen patients with sphenoid sinus aspergilloma were encountered. Complete medical documentation was available for only seven patients. Demographic data, medical history, predisposing factors, presenting signs and symptoms and neurological status were reviewed. Radiological findings including computed tomography (CT) and/or magnetic resonance (MR) were examined. In all patients, trans-sphenoidal microsurgical procedure was performed due to the presence of either pituitary adenoma or sphenoid-sellar lesion resembling a pituitary mass lesion. Specimens acquired underwent histopathological and microbiological analysis. After surgical treatment, patients were treated with antifungal medication and antibiotics according to the microbiological finding.

Results

Three patients—out of a total of seven enrolled——presented with isolated sphenoid sinus aspergilloma, while four patients presented with pituitary macroadenoma and sphenoid aspergilloma. Clinical features of these patients are listed in Table 1.

There were five women and two men patients. The mean age was 70.14 years (range, 54–87 years). Follow-up ranged from 6 to 36 months.

All patients underwent neuroradiological examination (MR and/or CT). Radiological characteristics are listed in Table 2. The only case where the preoperative diagnosis of possible sphenoid sinus aspergilloma was suspected according to the MR finding was in patient no. 7 (Figs. 1 and 2).

All patients underwent a trans-sphenoidal microsurgical approach. In three patients with isolated sphenoid sinus aspergilloma, upon opening the sphenoid sinus homogenous mucus extruded spontaneously, resembling a mucocele. After removing the mucus, a clay-like mass was found and removed. Specimens were sent for pathohistological and microbiological analysis. The sellar floor of the patient with non-Hodgkin lymphoma was completely destroyed, while the dura was dense but not showing signs of dural infiltration.

As for the patients with pitutary macroadenoma, upon entering the sphenoid sinus, a thickened mucosa was found, and the sinus was filled with a brownish amorphous mass. The sphenoid sinus mucosa and the mass were removed completely and the specimens were sent for pathohistological and microbiological analysis. In patients nos. 3, 6 and 7, the procedure continued with opening of the sellar dura and removing the pituitary macroadenoma. In patient no. 4, the procedure was discontinued based on a warning from a pathologist indicating that the sphenoid sinus specimen contained densely clustered *Aspergillus* hyphae, which may expose to the risk of intracranial fungal spread should the intrasellar compartment be opened. The patient was treated with voriconazole for 2 weeks. Three weeks after the first surgery, the patient was re-operated on and the pituitary macroprolactinoma was removed.

Pathohistological analysis revealed clustered *Aspergillus* hyphae and infiltrated sphenoid sinus mucosa in all patients (Fig. 3). Microbiological analysis revealed colonisation with single and dual bacterial species. All patients were treated with antimycotics, mainly voriconazole. Due to densely clustered hyphae, patient no. 4. was treated with itraconazole. Patients nos. 1, 2, 6 and 7 were also treated with orbenin and amoxicillin.

Postoperatively, patients showed improved neurological and endocrinological status without adverse events, postoperative complications and aspergilloma recurrence. Two patients died during follow-up as a result of complications related to their diseases, clivus chordoma and non-Hodgkin lymphoma.

Discussion

Fungal infections in the central nervous system (CNS) are increasingly being detected in neurosurgical patients due to longer survival of immunocompromised patients and larger ageing population [10].

CNS fungal infections are well documented. However, fungal granulomas are rare. The most common locations include the frontal lobe, anterior cranial fossa, middle cranial fossa and sellar region [10, 30].

Isolated sphenoid sinus aspergilloma (ISSA) is rare and difficult to diagnose due to a lack of typical signs of disease [12, 19, 24, 29].

Sphenoid sinus aspergillosis has been divided in four categories. The first two categories are considered invasive and include a fulminant and indolent form. The other two categories are considered non-invasive and include a mycetoma (aspergilloma) and allergic *Aspergillus* sinusitis [5, 7, 14, 20, 27].

Lee et al. [22] reported a series of 12 ISSA patients. Bowman et al. [6] reported 13 ISSA patients, whereas the largest series of 30 ISSA patients was reported by Jung et al. [19]. In all these series, the mean age was above 50 years.

In our series of seven patients, the mean age was 70, confirming the predilection of sphenoid sinus aspergilloma in individuals of advanced age. Also, there were five female patients, which corresponds to other series reporting female predominance [6, 23].

Parker et al. [26] and Shaw et al. [31] in their report suggested the significant correlation between isolated fungal sinusitis and immunocompromised patients. Dubey et al. [10] reported that diabetes mellitus (DM) was the most immunocompromising factor and present in 40 % of reported patients with CNS fungal infections. Three patients in our series were immunocompromised and two of them had DM. Both DM patients had an isolated sphenoid sinus

Table 1 Patients' clinical features and outcomes

	Gender	Age	History	Immunological status	Clinical features	Pathology location	Pathology/ microbiology	Therapy	Outcome after surgery	Follow-up (months)
1	M	54	Hypertension/DM Clivus chordoma surgery	Compromised	Left ophtalmoplegia Diplopia	Sphenoid sinus residual tumour bone infiltration	Aspergilloma *S. aureus*	Voriconazole Cloxacillin	Neurological improvement	14 (patient died)
2	M	87	NHL-FCC/AF	Compromised	Left ophtalmoplegia Diplopia	Sphenoid sinus Epidural infrasellar Ethmoid cells	Aspergilloma *S. aureus*	Voriconazole Cloxacillin	Neurological improvement	6 (patient died)
3	F	47	Appendectomy	Not compromised	Normal neurological exam Acromegaly	Sphenoid sinus intrasellar and suprasellar	Aspergilloma Growth hormone macroadenoma	Voriconazole	Endocrinological normalisation	36
4	F	78	CVI/hypertension/ duodenal ulcus	Not compromised	Diplopia Hyperprolactinaemia	Sphenoid sinus Intrasellar and suprasellar	Aspergilloma Macroprolactinoma	Voriconazole Itraconazole	Endocrinological normalisation	24
5	F	74	DM/hysterectomy Cholecystectomy	Compromised	Normal neurology and endocrinology exam	Sphenoid sinus	Aspergilloma	Voriconazole	No neurological or endocrinological deficit	24
6	F	76	Osteoporosis	Not compromised	Normal neurology and endocrinology exam	Sphenoid sinus intrasellar	Aspergilloma NF macroadenoma *P. mirabillis*	Voriconazole Amoxicillin/ Clavulanic acid	No neurological deficit Trombocitopenia	36
7	F	75	Hypertension	Not compromised	Left ophtalmoplegia Diplopia Hypopituitarism	Sphenoid sinus Intra and suprasellar	Aspergilloma NF macroadenoma *P. aeruginosa* *S. aureus*	Voriconazole Amoxicillin/ Clavulanic acid	Neurological improvement	36

CT computed tomography, *MR* magnetic resonance, *DM* diabetes mellitus, *NHL-FCC* non-Hodgkin's lymphoma of follicular centre cell type, *AF* atrial fibrillation, *NF* non functional, *CVI* cerebrovascular insult

Table 2 Preoperative radiographic and intraoperative findings

Patient	Radiographic examination	Intraoperative findings	Pathology location				Bone erosion	Pituitary adenoma (dimensions/mm)
			Sphenoid	Sellar	Suprasellar	Cavernous sinus		
1	MRI: homogenous mass obliterating the sphenoid sinus, residual tumour infiltrating the ethmoid cells, clivus and sellar dorsum, expanding intrasellar and suprasellar	Sphenoid sinus filled with necrotic soft mass not infiltrating surrounding structures, postoperative anatomical changes from the previous procedure and residual tumour (chordoma)	+	+	+	+	+	–[a]
2	CT: sphenoid sinus filled with homogenous mass with sellar bone destruction with a compression on the pituitary	Sphenoid sinus and ethmoid cells partially filled with amorphous mass, dura not infiltrated	+	+	+	–	+	–
3	MRI: intrasellar lesion with suprasellar expansion and chiasm elevation	Sphenoid sinus mucosa thickening, partially filled with brown amorphous mass, thinned anterior sellar wall, dura not infiltrated	+	+	+	–	–	+ (18×1-5×13)
4	MR: sellar dorsum bone destruction, intra and suprasellar process with necrotic avascular areas, involvement of the sphenoid sinus	Sphenoid sinus partially filled with soft amorphous mass which is not infiltrating the surrounding structures, thickened oedematous sphenoidal mucosa, intact dura	+	+	+	+	+	+ (28×1-9×22)
5	MRI/CT: lesion in the sphenoid sinus, no infiltration of surrounding structures	Sphenoid sinus partially filled with mass of thick fibrin membrane containing yellow purulent liquid	+	–	–	–	–	–
6	MRI: expansive infiltrative intrasellar mass with sellar floor bone erosion	Small fragments of amorphous brown soft mass in the sphenoid sinus, anterior sellar wall and dura infiltrated with the tumour	+	+	–	–	+	+ (22×1-5×12)
7	MRI/MSCT: intrasellar and suprasellar lesion, compressing the floor of the III ventricle, infiltrating left cavernous sinus and penetrating into the sphenoid sinus, inhomogenous cystic-necrotic areas with some haemosiderin deposits	Oedematous sphenoid mucosa, sinus cavity partially filled with grey-yellow solid tissue, sellar wall infiltrated with the tumour	+	+	+	+	+	+ (35×1-6×25)

[a] Patient operated on 3 years previously for clivus chordoma

aspergilloma—one with a silent clinical form and the other with ocular-orbital symptoms.

Sphenoid sinus aspergillosis, in a non-invasive form, can arise in an immunocompetent patient [11]. Four patients in our series were immunocompetent and had a mycetoma form of sphenoid sinus aspergillosis found accidentally during the pituitary macroadenoma surgery.

Three patients presented with ocular-orbital symptoms and in all three patients symptoms developed rapidly and may be interpreted as a result of compression of the cranial nerves, mainly in the cavernous sinus, due to increased pressure in the sphenoid sinus caused by fungal infection or by adenoma invagination towards the cavernous sinus.

This is in correlation with other series where visual disturbances have been reported to occur in 24–50 % of ISSA patients, while diplopia has been observed in 40 % of ISSA cases [15, 22].

Presumption of sphenoid sinus aspergilloma can be done based on the radiological findings. MR is a primary tool in imaging of pituitary adenomas. Aspergillosis of sinonasal origin has typical MRI features of a mass lesion, producing hypo-intense to iso-intense signals on T1-weighted images and hypo-intensity on T2-weighted images, with bright homogenous peripheral contrast enhancement. Yamada et al. [33] described low intensity zones within the hyper-intense mass as zones of iron accumulation, the preferred places for *Aspergillus* proliferation. All patients in our series had MR and/or CT scans. In two patients with normal neurological and endocrinological status, MR/CT was performed due to non-specific symptoms, and the finding of ISSA and a

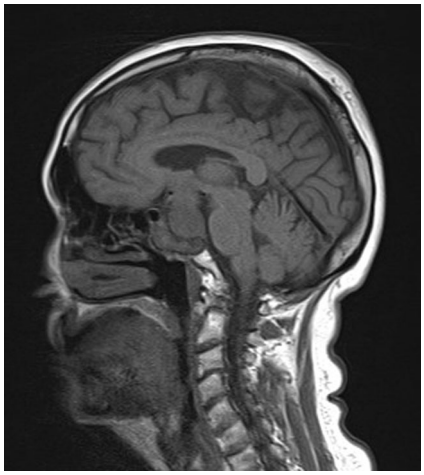

Fig. 1 Preoperative MR of the brain. Native sagittal T1-weighted imaging. An iso-intense mass lesion is occupying the sellar and suprasellar region. A mass lesion is present in the sphenoid sinus. Note the relatively clear border between the sellar and sphenoid lesion. The sellar and suprasellar lesion represents the pituitary macroadenoma. Mass lesion in the sphenoid sinus represents dense sphenoid mucosa with aspergilloma

macroadenoma was incidental. According to the MR finding, the preoperative assumption of possible sphenoid sinus aspergilloma was made in only one patient.

Definitive diagnosis of sphenoid sinus aspergilloma is based on histopathological analysis [7]. An interesting feature found in our series was a positive microbiological finding of *Staphylococcus aureus* in two immunocompromised patients with ISSA. *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Proteus mirabilis* were positive in two patients with sphenoid

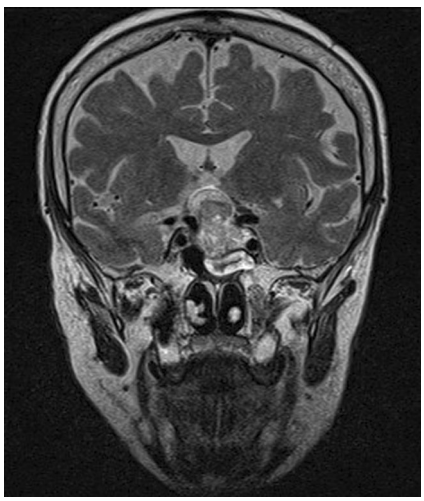

Fig. 2 Preoperative MRI of the brain. Native coronal T2-weighted imaging. Pituitary macroadenoma extending in the suprasellar space dislocating the optic chiasm. Note the extension of the adenoma in the left cavernous sinus. A hyper-intense mass lesion is present in the sphenoid sinus representing sphenoid sinus aspergilloma

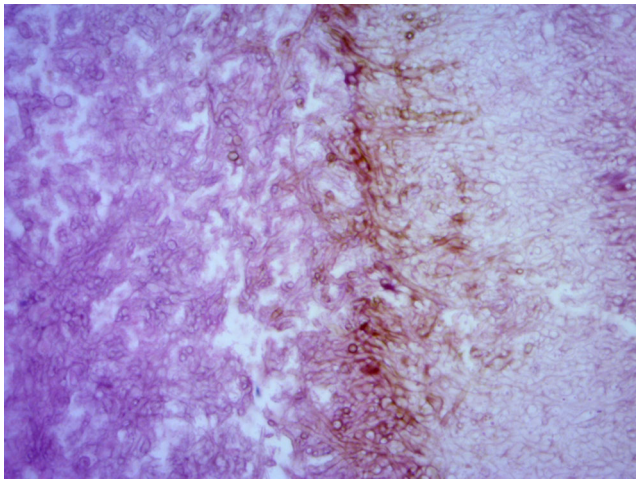

Fig. 3 Photomicrograph of the surgical specimen revealing the histopathological findings of dense and clustered hyphae characteristic for aspergillosis (haematoxylin and eosin, ×400)

aspergilloma and macroadenoma. Non-monomicrobial cases could be explained by prior sphenoid sinus bacterial colonisation and decreased aeration of the sinus [32]. This is of importance, especially in cases of sellar invasion and immunosuppression where complications such as meningitis could be expected.

Endonasal endoscopic sphenoidotomy is considered a treatment of choice in cases of ISSA [6, 9]. In cases of sphenoid aspergilloma and pituitary adenoma a microsurgical or endoscopic trans-sphenoidal procedure is recommended. Surgery alone without antifungal treatment achieves good results in non-invasive forms as reported by Bowman et al. [22], Lee et al. [6] and Pagella et al. [25].

Invasive forms require surgical treatment and antifungal medications [4]. All of our patients underwent endonasal trans-sphenoidal microsurgical treatment and received antifungal medications. Four patients with positive microbiological finding also received antibiotics.

There are only four reported cases of a sphenoid sinus aspergilloma associated with a pituitary adenoma [1, 3, 8, 13] (Table 3). Our series comprise four surgically treated patients with macroadenoma presenting as acromegaly, hyperprolactinaemia and hypopituitarism. Sphenoid sinus aspergilloma was an incidental finding encountered intraoperatively.

Although cases of isolated sphenoid sinus aspergilloma and incidental finding of aspergilloma during pituitary surgery can be considered a different entity, we have included those cases into one series. The aim was to emphasise the possibility of sphenoid sinus aspergilloma appearance when dealing with a sphenoid-sellar mass lesions, especially due to the fact that aspergillosis found during trans-sphenoidal surgery is probably underdiagnosed [21].

Table 3 Reported cases of pituitary adenoma and sphenoid sinus aspergilloma coexistence

Author	Description
Furtado et al. [1]	Acromegaly due to GH-secreting pituitary adenoma+sphenocavernous aspergilloma
Bridenstine et al. [7]	Cushing's disease due to mixed adenoma-gangliocytoma of posterior pituitary+sphenoid sinus aspergilloma
Ahmeti et al. [2]	NF pituitary adenoma+sphenoid sinus aspergilloma
Azarpira et al. [3]	NF pituitary adenoma with signs of apoplexy+sphenoid sinus aspergillosis

GH growth hormone, *NF* non-functional

Conclusions

Isolated sphenoid sinus aspergilloma is a rare condition. The simultaneous appearance of sphenoid aspergilloma and pituitary adenoma is even a rarer occurrence; however, it should be taken into consideration in elderly female patients, both immunocompetent or immunosuppressed, presenting with mass lesion in the sphenoid sinus and sellar region.

Trans-nasal trans-sphenoidal surgery, including thorough sphenoidal extirpation and adenomectomy is a treatment of choice, and in most cases is the sole treatment.

In order to prevent serious complications in invasive aspergilloma cases showing positive microbiological findings, antimycotics and antibiotics should be combined with surgical treatment.

Conflicts of interest None.

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Comments

This paper by Sajko et al. touches an important issue in pituitary surgery: not every space-occupying lesion (SOL) that appears to be a pituitary adenoma (PA) preoperatively turns out to be a PA postoperatively. The rate of unexpected histology in presumably endocrine inactive PA may be as high as 18 % [1]. Typically, endocrine inactive PA are tumours of an advanced age [2]. Interestingly, the patients with a suspected endocrine inactive PA who finally turned out to have an unexpected histology also seem to belong to the advanced age group [1]. Sajko et al. found aspergilloma in trans-sphenoidal surgery for presumed PA in basically 1.3 % of their total of about 1,000 cases. If one assumes a normal distribution of PA coming to trans-sphenoidal surgery at their institution, about 27 % would be endocrine inactive [2]. Since cases of intrasellar or parasellar aspergilloma are unlikely to present as endocrine active PA, it is probably safe to assume that the majority of the 13 patients with aspergilloma presented preoperatively as endocrine inactive PA. With this in mind, one may expect a 3–4 % rate of aspergilloma in all presumed endocrine inactive PA at the authors' institution. This rate may even be higher in less developed regions. Just as the patients with endocrine inactive PA, the patients with intrasellar or parasellar aspergilloma were of an advanced age group. The authors found a preponderance for females, which was not the case for neoplastic unexpected histologies [1]. Diabetes mellitus or immunodeficiency was present in almost half of their patients with aspergilloma. Just as the authors conclude, awareness should be heightened especially in elderly female patients presenting with a SOL in the sphenoid sinus and the sellar region. The authors are not the first to report on aspergilloma in the sellar region [3], but they certainly are the first to present a systematic review of this non-neoplastic SOL mimicking PA in their own large neurosurgical patient cohort. It is of great importance to pituitary surgeons to be aware that not every SOL which preoperatively seems to be a PA is necessarily a PA and that it may not even be a neoplastic lesion. This awareness adds to the patients' security, since some of those unexpected lesions may require alternative surgical strategies from the conventional PA surgery. This manuscript underscores the need to approach "pituitary" patients with an open mind.

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