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Short Illustrated Review

Primary aspergillosis of the sphenoid sinus with pituitary invasion – a rare differential diagnosis of sellar lesions

T. Pinzer[1], **M. Reiß**[2], **H. Bourquain**[3], **K. G. Krishnan**[1], and **G. Schackert**[1]

[1] Klinik und Poliklinik für Neurochirurgie, Universitätsklinikum Dresden, Dresden, Germany
[2] Klinik für HNO, Elblandkliniken, Radebeul-Meissen, Germany
[3] Abteilung für Neuroradiologie, Universitätsklinikum Dresden, Dresden, Germany

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Summary

Aspergillosis belongs to the group of mycotic diseases of paranasal sinuses. The invasive forms, and particularly the fulminant forms, are potentially fatal. Isolated aspergillosis of the sphenoid sinus or the clivus is a difficult diagnosis, since the often misleading clinical manifestations of this rare disease develop late. These patients become apparent by neurological signs such as cavernous sinus syndrome, pseudotumor of the pituitary or the orbit. Diagnosis is often made intra-operatively or on histological examination.

We report a case of invasive aspergillosis uniquely involving the sellar area revealed by clinical features suggesting a pseudotumor of the pituitary. Although such lesions are almost always seen in immune suppressed subjects, in our case, the patient was immune competent and had no past history of sinusitis.

The question of whether, and when to perform limited or extensive surgery remains an issue for discussion, owing to the rarity of this disease honed by lack of experience. It depends on several factors: the kind of disease, the immunity, the subtype of invasive fungal sinusitis and the degree of tissue invasion.

Keywords: Aspergillosis; skull base; pituitary adenoma; diseases of the paranasal sinuses.

Introduction

Aspergillosis of the sphenoid sinus or the clivus, as a rule, becomes apparent through neurological symptoms and signs, such as cavernous sinus syndrome or pseudotumor of the pituitary or the orbit. Mostly the diagnosis of aspergillosis is made intra-operatively or on histological examination of the specimen. A fulminant form of this disease can destroy the bone and/or invade the cavernous sinus and the meninges. The invasive forms are usually observed in immune compromised patients. Fungi of the species Aspergillus and the class Ascomycetes are present worldwide [25]. Out of over 300 existent species, human diseases are often caused by *Aspergillus niger*, *flavus* and *fumigatus*. The aspergillus species' that are pathogenic to humans are found to exist in a saprophytic fashion in the upper respiratory tract mucosa. The *loci minores resistentiae* for the manifestation of aspergillosis are the lungs and, exceptionally, the paranasal sinuses [19]. The clinical manifestation of such mycoses is through non-specific rhinosinusitis accompanied by rhinorrhoea and an obstructed nasal airway [3, 4, 6, 11, 14, 15, 23, 26].

The incidence of the saprophytic form is found to be quite variable: a statistical rate of 2–10% of all patients suffering chronic paranasal sinus diseases are shown to harbour a saprophytic mycosis [25]. Invasive aspergillosis of the paranasal sinuses is a rarity. It tends to manifest itself with severe headache or primary ophthalmological symptoms and signs, such as loss of visual acuity, exophthalmos and/or diplopia, and thus divert the physician towards the diagnosis of malignant space occupying lesions [3, 16, 19, 25]. Since its first description by Schubert in 1885, the diagnosis of aspergillusmycosis of the nose and the paranasal sinuses has become more frequent [22]. Such events are, as a rule, observed in individuals with a compromised immune system, through infections, congenital or drug induced immune deficiency, consuming malignancies or *diabetes*

mellitus. However, there are also single reports of aspergillosis in patients without a documented immune deficiency [25].

Literature review

The literature used for this review was identified using the Medline database (PubMed, http://www.ncbi.nlm.nih.gov/PubMed/). The following English keywords were used for the search: aspergillosis, sella and pituitary gland. Manual searching of journals was conducted for the term 'aspergillosis', and several cross references from the articles were scrutinized. Owing to possible modifications in drug therapy regimes, only references dating back no earlier than 1986 were considered. Four articles were identified to report on intrasellar or sellar aspergillous invasion presenting as a pituitary mass [15–17, 20]. Among them only one case report showed a similar strategy as presented in this report [17].

Analysis

Aspergillosis of the sphenoid sinus extending into the sellar region and simulating a pituitary tumor is extremely rare. Only four such cases have been reported in the English literature [15–17, 20]. Three cases-the case of Ramos-Gabatin and Jordan [17] and of Scanarini *et al.* [20] and the present case describe primary intrasellar fungal invasion that appeared to be pituitary tumors in imaging modalities. Aspergillous infections usually invade the paranasal sinuses [4, 6, 12, 18, 19, 26]. Not infrequently the infection extends into the orbital region [8–11, 18], where it may involve the optic nerve [9, 10]. Reports on invasion of the skull base regions of the vicinity were also published [2, 5, 21, 23, 24]. Fungal infections of the paranasal sinuses, especially with skull base extension were found to occur exclusively in the immune deficient or in patients with cancer or bone marrow transplants. In contrast to the cases presented in the literature, we could not detect any possible immune deficiency in our patient. This fact stresses the necessity of including invasive aspergillosis in the differential diagnosis to pituitary tumors.

Illustrative case

A 59 year old caucasian female was admitted to the hospital due to a change in the character of her migraine attacks. The patient had a permanent left sided hemicephalgia, where even strong analgetic drugs (including opioid medication) offered only a short time of relief. Administration of corticosteroids brought about a steady reduction in headache.

The history failed to reveal any known disease. There were no implications of a malignant disease or an immune suppressed status or a

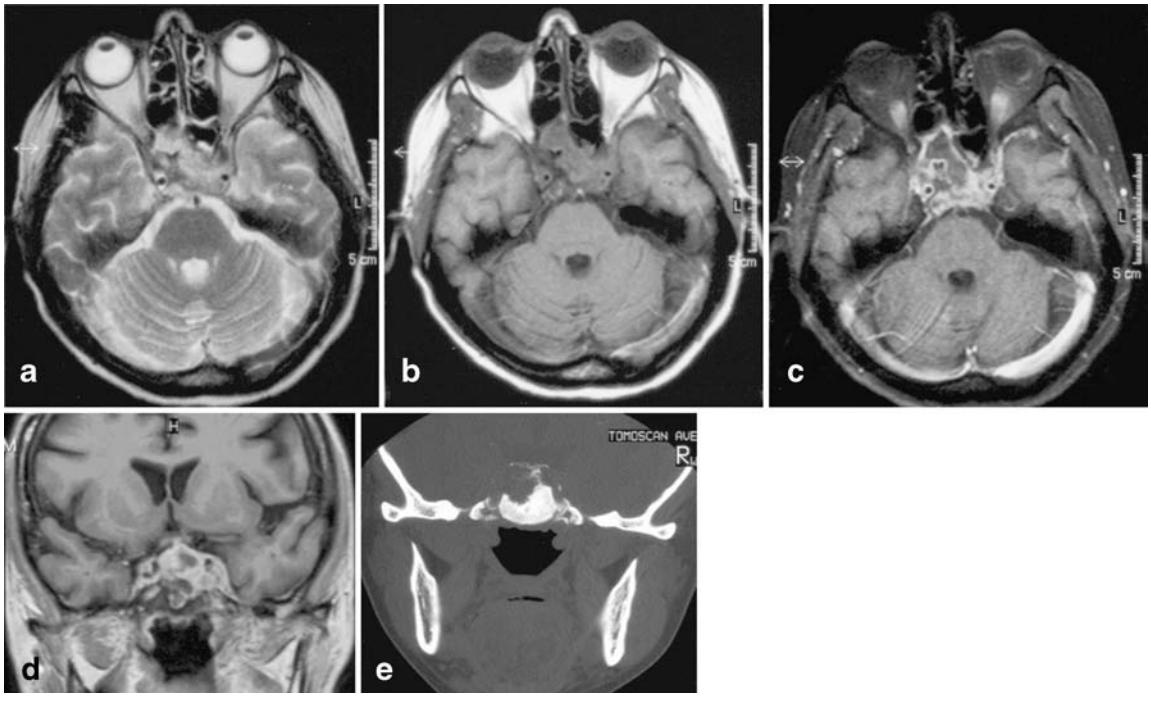

Fig. 1. (a) T2 weighted imaging sequences revealed a hyperintense intrasellar space occupying lesion that infiltrated the cavernous sinus from the left side, whereas (b) in the T1 weighted sequences before contrast medium infusion, this tumor showed an iso-intense signal (in comparison to the grey matter). (c) After contrast medium the tumor showed a strong, border enhancement with several septal structures. (d) The infiltration of the cavernous sinus is best seen in the coronal slices. (e) Shows the extent of bone destruction of the dorsum sellae (notice the left side)

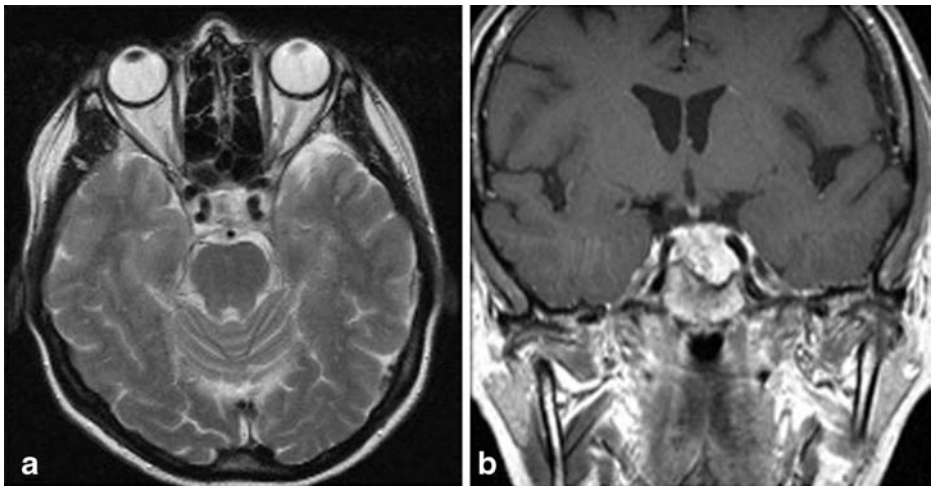

Fig. 2. (a) Postoperative T2 weighted images showing inhomogenous, CSF-iso-intense and slightly hypo-intense intrasellar tissue. (b) Contrast medium enhances the structure homogenously. The bulge in the sphenoid sinus is seen clearly. These are signs of scar tissue after debridément of the intrasellar lesion

paranasal disease focus. There were no specific symptoms on history taking and examination. However, left sided abducent nerve palsy was apparent on neuroophthalmological work-up. Blood sampling showed an imminent leucocytosis (18 GPt/l) and a slight increase in the ESR (13/33). Other parameters, including C-reactive protein, were normal. Neuro-endocrinological studies showed a fall in serum TSH and cortisol levels. An ear, nose and throat work-up failed to reveal any pathology of the paranasal sinus. Computer tomography (CT) and magnetic resonance imaging (MRI) of the skull showed a partially cystic and partially solid space occupying lesion about 2 cm in diameter in the pituitary area with an invasive growth into the surrounding structures, especially on the left side. The cavernous sinus was infiltrated and the dorsum sellae was found to be destroyed. Furthermore, mucosal edema of the sphenoid sinus was apparent (Fig. 1).

We performed a transsphenoidal approach to the lesion, which released necrotic, detritic material from the sphenoidal sinus. After debridèment of the inflammed mucosa, it became apparent that the sellar bone was completely destroyed sparing a small remnant on the right side. Necrotic, detritus or caseous material, as found in the sphenoidal sinus, could further be removed from the sellar cavity proper. No capsule was found. A CSF-leak did not occur.

The histological work-up failed to show any tumor tissue, however it confirmed chronic inflammatory material with massive fungal hyphi. Microbiological studies revealed neither aerobes nor anaerobes in the specimen.

The postoperative course was uneventful. Serological studies did not show any systemic mycotic, including aspergillus, infection. Due to the histological diagnosis of aspergillosis, the patient received antimycotic drugs (Itraconazol, Sempera®) for 12 weeks. Both the headache and the abducent nerve palsy disappeared completely after surgery. The patient has remained symptom free for more than 6 years. There was no pathological substrate seen in the paranasal sinuses. Follow-up MRI studies (six months after surgery) showed scar tissue in the intrasellar area, the sphenoidal sinus and the left cavernous sinus; there were no hints of inflamed tissue in the respective areas (Fig. 2).

Discussion

The reported case shows us several interesting specificities. For one it is remarkable that the patient did not show any nasal symptoms, such as putrid secretions, mucosal polyposis or nasal obstruction, that are described by other authors [4, 7, 8]. Secondly, a tumor was suspected on neuro-imaging. Thirdly, even after incomplete resection of the mycotic lesion, complete healing was achieved using systemic antimycotic therapy with Itraconazol. Furthermore, it is curious that an invasive mycotic infection was found in a patient without any recognizable systemic immune deficiency.

Mycotic diseases and immune status

Mycotic diseases of the paranasal sinuses differentiate invasive and non-invasive forms, depending on the extent of tissue invasion [27]. Which form is prevalent in a patient is dependent on the immune status. Non-fulminant forms are usually present in immune competent patients.

First of all, disease of the haemopoietic system, especially granulocytopenias, is one of the predisposing factors for acute invasive and fulminant aspergillosis. It is known that neutrophils play a major role in the cellular immune defence against fungal infections [1]. Owing to this reason, neutropenic patients are especially prone to mycoses. Other risk factors are immune deficiency syndromes (HIV) [11, 27] and iatrogenically induced immune suppressive status after organ and bone marrow transplantation [7, 21].

Clinical symptoms

The symptoms of invasive aspergillosis are dependent on the type and extent of destruction of the anatomical

structures. Not seldom-as in our case-ocular muscle paresis with diplopia, to the extent of ophthalmoplegia and ptosis are seen in a cavernous sinus syndrome. Suprasellar invasion may cause visual acuity and field loss, even to the extent of blindness. Non-specific headache or pyrexia were reported in all the cases published so far [2, 10, 13, 18, 19, 25]. Blood sampling reportedly shows an inflammatory reaction [15, 16], whereas immune suppressed patients show a neutropenia [19]. In specific cases an endocrine dysfunction may be expected [2].

Imaging studies

Imaging studies may reveal a dilated sella and bone destruction, even in the plain skull X-ray films [13, 15]. The diagnostic work-up of an invasive mycotic sinusitis, especially with suspected frontobasal or intracranial spread, calls for a CT imaging of the paranasal sinuses and skull base, as well as MRI [3, 4, 13, 15, 20, 24]. Computer tomography shows an intrasphenoidal and intra sellar soft tissue mass with calcification, as well as destruction of the surrounding bone tissue [13, 25]. Magnetic resonance tomography reveals different types of lesions. Aspergillomas are seen as a characteristically hypodense lesion both in T1 and T2 weighted sequences, which is quite typical for a fungal invasion [13, 25]. Angiography shows the lesion as a vascular [13].

The result of such diagnosis is quite non-specific, and, owing to its rarity, such a lesion may be misinterpreted as a pituitary adenoma or, in case of advanced bone destruction, as a malignant tumor [13, 15, 17, 25].

Surgical treatment

The final diagnosis of an aspergillus infection of the frontal skull base is only made as a result of surgical exploration of the invaded areas. In most of the cases detritic mucosal masses are found to fill the paranasal sinuses. The surrounding mucosa is found inflammed and edematous. In some cases a putrid secretion may be present, whereas this does not specify the formation of an aspergilloma. It could also denote the various phases of sinusitis aspergillosa. In our case, the computer tomography showed edema of the sphenoid sinus mucosa, whereas surgical exploration disclosed the presence of caseous masses in the sinus [4, 15–17].

Surgical treatment should aim more at radically removing the mycotic infected lesion, rather than draining it. Especially by the invasive and fulminant variations of paranasal and skull base aspergillosis, it is of high priority to radically remove the involved structures. This is particularly necessary in ''immune'' compromised individuals [13, 15, 16, 23, 25]. However, it is important to consider the bleeding risk in immune suppressed patients with lowered platelet count [5, 15, 19]. The surgical intervention should be planned as soon as the diagnosis of aspergillosis is suspected in order to prevent a spontaneous intradural invasion [13]. The risks of the surgical procedure are damage to the orbit, brain and cranial nerves, and, above all, injury to the dura mater and the possibility of intracranial spread of the infection [19]. In such a case, the surgical exploration might as well risk the wide intracranial spread of the infection to the orbit, frontal base and even the clivus [3, 7, 9, 11, 18, 24, 26]. It should also be considered that surgery itself is a stress factor for the immune compromised patient [8, 15]. Kennedy *et al.* retrospectively compared 26 patients who were surgically treated with either drainage or extensive resection and found out that extensive resection should not necessarily mean more effectiveness than drainage procedures [12]. Landoy *et al.* propose that surgical exploration should be avoided in patients with other serious accompanying diseases [14]. On the contrary, Chang *et al.* [4] and De Foer *et al.* [6] suggest an extensive debridément of the involved structures in invasive and fulminant forms of aspergillosis. Furthermore, Yumuto *et al.* [26] prefer even an orbital exenteration in cases of orbital involvement.

Drug therapy

Local lavage with Fluconazol through an implanted drain [13], as well as second look surgery have been reported [19]. There seems an unanimous opinion in the literature about the transsphenoidal approach, since this minimizes the risk of cerebro spinal fluid contamination [13, 15, 17, 20, 23, 25]. If, for some reason, a macroscopically total resection is not possible, an antimycotic therapy should be introduced in any case. For this purpose various drugs have been reported upon, e.g. Amphotericin B, Flucytosin (Ancotil®), Rifampicin (Rifa®), lipid-capsuled Amphotericin B® (AmBisome®), Itraconazole (Sempera®) and Caspofungin (Cancidas®). Recently a broad spectrum triazole-antymycotic drug, Voricanozole (VFEND®) has become available. This has proved to be more effective than the others, especially in invasive forms of aspergillosis in patients with risk factors, such as poor general prognosis and immune compromised status, since the survival rate and the side-effect free therapy window is larger.

The value of postoperative antimycotic therapy is discussed in a controversial manner. Some reports consider postoperative systemic antimycotic therapy as superfluous in case of total macroscopic extirpation of an invasive aspergillosis without intradural involvement [13, 15]. However, intradural spread is found to definitely call for such an adjuvant [13, 25]. Many authors approve of a combination of surgical and postoperative systemic antimycotic therapy [5, 19, 23, 24]. Streppel *et al.* report on a case, where drug therapy using lipid-capsulated Amphotericin B combined with Itraconazole led to complete cure in a female patient with intracranial mycotic spread [23]. Fatal outcomes are reported, if postoperative antimycotic therapy after incomplete resection still leads to progression of the disease [23].

Stabilization of the immune status in compromised patients seems to play an important role in the general treatment strategy, the aim being to increase the number of granulocytes, for instance, through administration of granulocyte colony stimulating factors [19].

Follow-up strategy

The overall mortality rate of this disease, which has not been uniformly reported in the literature, constitutes around 75%. Impressively, the relapse rate in immune compromised patients is found to be over 50% [11, 12, 19, 21, 27]. All these facts support the strategy of postoperative, prophylactic long-term treatment using antimycotic drugs as well as control imaging studies. Control studies are best performed using magnetic resonance imaging and scintigraphy with Gallium-67 [25]. Owing to the rarity of the disease, the overall experience on surgical treatment of invasive mycotic sinusitis seems to be very limited. The immune status is one of the most important prognostic factors for the outcome.

Since in the case we have presented here, an incomplete surgical resection combined with postoperative antimycotic drug therapy brought about complete remission of the disease, both clinically as well as radiologically, we may infer that such a form of management might be a sensible alternative to extensive surgical resection that risks the loss of important functions.

Conclusion

The case we discuss here stresses the importance and necessity of considering the possibility of invasive aspergillosis as a differential diagnosis to tumors, when non-specific symptoms combined with imaging studies reveal bone destruction of the skull base with mucosal edema and/or shading of the paranasal sinuses. The indication for surgical exploration depends on several factors, e.g. immune status and general condition of the patient, form of the invasive aspergillosis and the extent of tissue destruction. A timely administered systemic antimycotic therapy is a priority.

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Comments

This case report paper is timely reminder of a condition that we can expect to see more of in an era when the immuno compromised patient is seen more often. Aspergillous infection of the CNS is often considered a fatal condition, so that if it exists in the nasal sinuses, although very rare, it should be both considered as part of the differential diagnosis of an unusual lesion in the parasellar area (quite far down the list of possible diagnoses!) and a biopsy decompression that does not transgress the CSF is important. This case is unusual as the patient was not immuno compromised and did well.

Careful consideration of antifungal therapy must also be given as is discussed in this paper.

Michael Powell

This paper provides the readers with a comprehensive view of a problem which is encountered from time to time in the course of skull base surgery, particularly by the transsphenoidal route, for lesions of the anterior skull base. The problem of coexisting fungal infection of the sphenoid sinus is obviously a serious one and certainly can influence both the technical aspects of surgery and the outcome for the patient.

Aspergillosis has been encountered in the course of transsphenoidal removal of pituitary tumors twice in our experience. In one patient the infection was extensive and invaded the entire sinus system anteriorly. This patient successfully underwent removal of the bulk of the granulomatous lesion within the sinuses and had removal of his rather large pituitary macroadenoma as well. He required an extensive course of antifungal treatment following the guidelines that are clearly presented in this excellent paper. Our second patient presented with a fungus ball isolated within the sphenoid sinus. This was resected. The sinus was carefully irrigated clear and the patient then went on to have removal of a clinically non-functioning pituitary macroadenoma. Her postoperative course was uneventful and she did not require specific antifungal therapy and remains well in follow-up.

It is obvious that fungal infections vary from serious life-threatening infections, as is seen in mucormycosis, to relatively innocent incidental findings. The surgeon who encounters these challenges must be capable of making a fairly rapid assessment of the risks and benefits of continuing with surgery, and also considering the strategies for treating the underlying fungal lesion in an appropriate and diligent fashion.

This is a thought provoking article that will be of use to all surgeons who deal with lesions of the anterior skull base.

R. Laws
Charlottesville

Correspondence: Kartik G. Krishnan, Department of Neurological Surgery, Carl Gustav Carus University Hospital, Fetscherstrasse 74, D-01309 Dresden, Germany. e-mail: Kartik.Krishnan@uniklinikum-dresden.de