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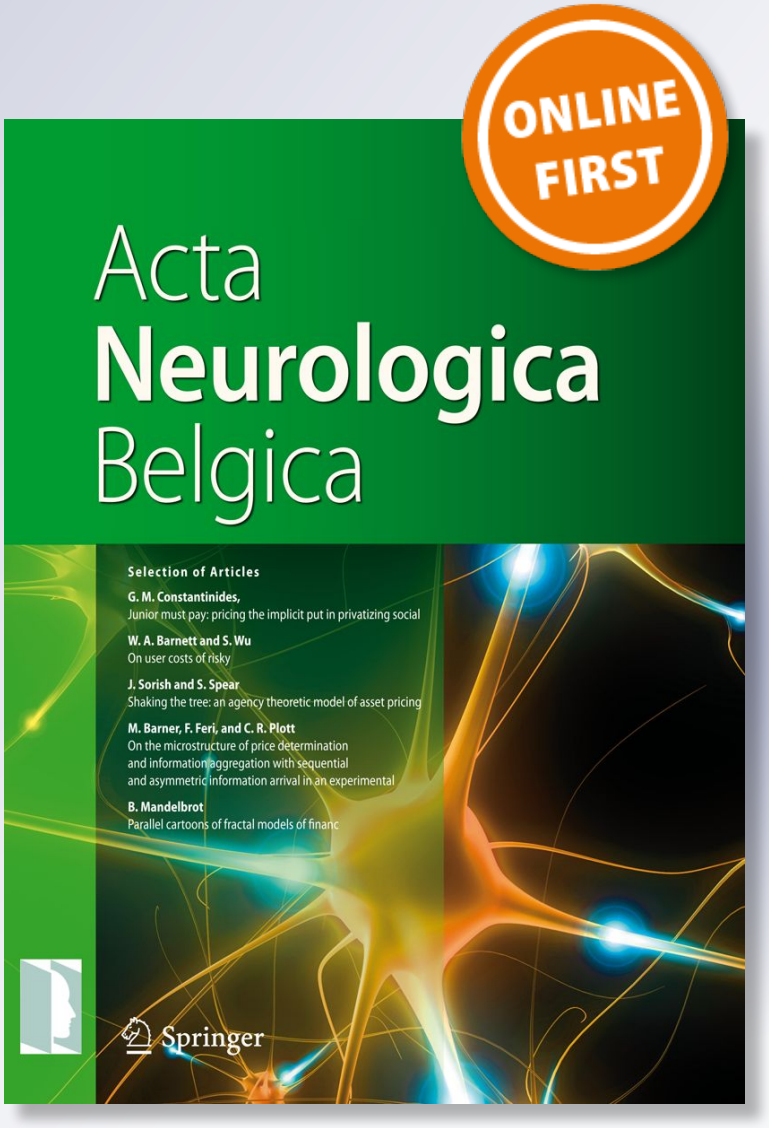

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ORIGINAL ARTICLE

Fatal rhinocerebral mucormycosis with intracavernous carotid aneurysm and thrombosis: a late complication of transsphenoidal surgery?

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Abstract Mucormycosis is a rare opportunistic fungal infection. Rhinocerebral form of the disease mainly affects diabetic or immunocompromised patients. Mucormycosis have specific tropism for blood vessels leading to mucorthrombosis and less often to mycotic aneurysms. We report on a patient initially presenting with a severe sphenoid sinusopathy, who progressively evolved to cavernous sinus syndrome, internal carotid aneurysm followed by spontaneous thrombosis, chronic meningitis and ultimately fatal hypertensive hydrocephalus. Necropsy revealed a purulent infiltrate containing thin-walled, aseptate, right-angle branching, hyphae consistent with mucormycosis. His only relevant previous medical history was a transsphenoidal surgery for pituitary macroadenoma 21 years before. We hypothesize that post-surgical mucosal changes in the sphenoid sinus have been a favoring factor for delayed and invasive mucor infection.

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Keywords Rhinocerebral mucormycosis · Carotid aneurysm · Mucorthrombosis · Transsphenoidal surgery

Introduction

Mucormycosis is a rare, usually acute, opportunistic invasive fungal infection declining in several clinical forms (rhino-orbital-cerebral, pulmonary, cutaneous or subcutaneous, gastrointestinal, disseminated and miscellaneous forms) [1–4]. The rhinocerebral form is the most frequent (40–50 %) of mucormycotic infections [1, 3] and mainly affects diabetic or immunocompromised patients.

Mucormycosis is caused by fungi from the class zygomycetes. The most frequent species involved in rhinocerebral mucormycosis is *Rhizopus oryzae* [1, 3, 5]. This saprophytic and ubiquitous fungus is present in soil, decaying matters, air and moist environment. It is the second filamentous fungal infection after *Aspergillus* [5]. Mucormycosis have some specific tropism for vascular wall, leading to mucorthrombosis and less often to true mycotic aneurysm [1, 3, 6, 18, 22, 26, 27].

We report on an unusual case of rhinocerebral mucormycosis in a patient presenting a 10-month history of sphenoid sinusopathy, progressive cavernous sinus syndrome, internal carotid aneurysm evolving to thrombosis, chronic meningitis and fatal hypertensive hydrocephalus. This patient had a transsphenoidal surgery 21 years before, for a pituitary macroadenoma.

Case report

A 64-year-old male patient sought medical advice in November 2006 for a right hemifacial pain and a

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homolateral nasal obstruction. He had a medical history of somatotropic macroadenoma treated by transsphenoidal surgery and local radiotherapy in 1985, resulting in an anterior pituitary deficiency treated with substitutive doses of hydrocortisone (10 + 15 mg), L-thyroxin, testosterone (Sustanon®) and somatotropin (Genotonorm®). A brain magnetic resonance (MR) imaging examination performed in December 2006 showed no evolution of the adenomatous residual tissue present for years. A discrete sphenoid sinusopathy was present (Fig. 1a). In January 2007, the facial pain was permanent and the patient complained of diplopia due to a right sixth nerve partial palsy. He also suffered from asthenia, loss of weight and depressive affects. In February 2007, episodic fever peaks occurred. A second brain MR examination (Figs. 1b, 2) revealed an extensive sphenoid sinusopathy, a huge fusiform aneurysmal dilatation of the right intracavernous internal carotid artery (ICA) and a suprasellar extension of the mass which was quiescent during previous observation periods. On brain CT scan, some inflammatory-induced bone modifications were observed as well as bone defects between sphenoid and cavernous sinuses (not illustrated). Blood tests showed a moderate inflammatory syndrome [C-reactive protein (CRP) 2.3 mg/dL normal range <0.1] without increase in the white blood cell (WBC) count. Recurrence of the somatotropic macroadenoma was first suspected and Genotonorm® was interrupted.

In May 2007, a third brain MRI performed just before a programmed aneurysm embolization showed a spontaneous and extensive carotid thrombosis without associated stroke (Fig. 3). In June 2007, the patient was readmitted for confusion, disorientation in time and space, apathy and fever. He still presented a right sixth nerve palsy, a right trigeminal hypoesthesia and facial neuralgia. CRP levels had increased up to 8.9 mg/dL. CSF analysis revealed a mild mononuclear pleocytosis (16 WBC/μL), a moderate increase in the protein content (76 mg/dL), but a normal glucose (44 mg/dL) and lactate levels (1.9 mmol/L). No specific oligoclonal IgG bands were found. CSF cultures and herpes simplex virus (HSV) polymerase chain reaction (PCR) were sterile or negative. Serologic blood tests for usual bacterial and viral infections were also negative. The patient was transferred to a rehabilitation center in July 2007. His clinical status worsened a few weeks later with intermittent pyrexia, cognitive impairment, disinhibition and urinary incontinence. A second CSF analysis showed 62 WBC/μL, high protein content (131 mg/dL), and a decreased glucose level (29 mg/dL) with the appearance of CSF-restricted oligoclonal IgG bands.

On 14 August 2007, he was transferred to our Department of Neurology. He presented meningeal signs, a right ptosis, complete right sixth nerve palsy and fluctuating consciousness level. CSF analysis showed a neutrophilic pleocytosis (22 WBC/μL), increased protein level (186 mg/dL) and elevated lactate (3.8 mmol/L). Brain MRI (Fig. 4) showed a florid pansinusopathy and a basal pachymeningitis involving the cavernous sinus, pituitary sella, interpeduncular cisterns, right trigeminal nerve and cerebellar tentorium, resulting in obstructive hypertensive hydrocephalus. A right thalamic infarction was also present. The clinical diagnosis was a mycotic cerebromeningitis starting from the sphenoid sinus and causing mycotic internal carotid aneurysm followed by spontaneous thrombosis. The patient died a few days later before any effective treatment could have been started.

Autopsy findings revealed a purulent abscess invading pituitary sella, sphenoid and ethmoid sinuses. Thrombosis of surrounding vessels was shown together with a large

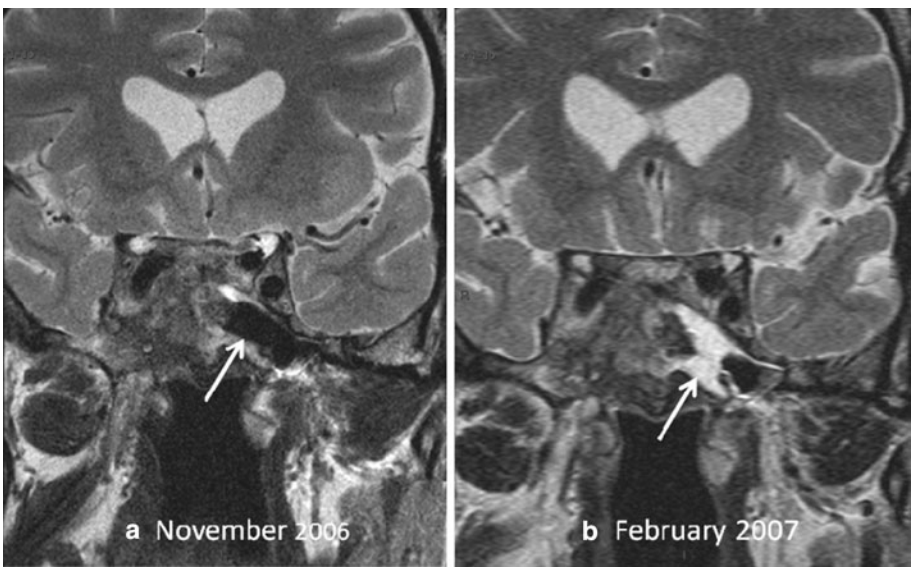

Fig. 1 FSE-T2-weighted coronal sections in similar slice location (December 2006 in **a** and February 2007 in **b**) evolution from thin hyperintense mucous thickening to an extensive submucous oedema of sphenoid sinus (*arrows*). Observe subtle bone changes due to previous surgery

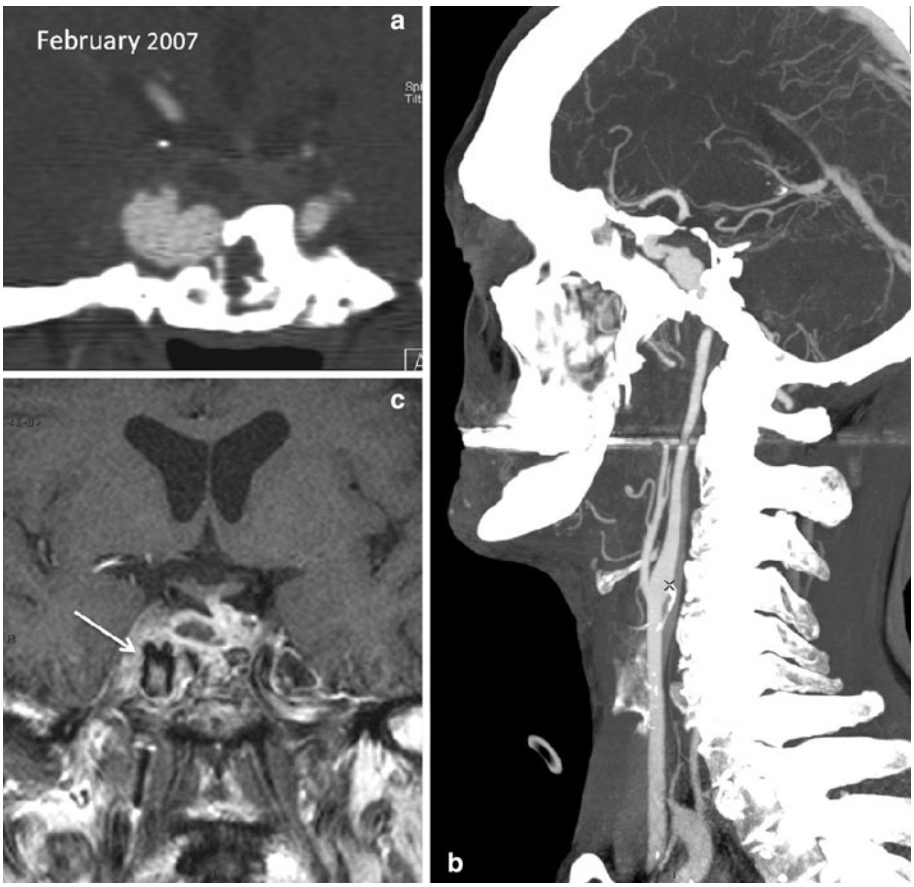

Fig. 2 Imaging work-up in February 2007 demonstrating the onset of intracavernous mycotic aneurysm of the ICA: CT angiography in **a** (coronal reformat at sphenoid level) and **b** (sagittal reformat covering head and neck): focal enlargement of the lumen of the vessel is obvious. Contrast-enhanced coronal T1-weighted view in **c** showing enlarged lumen of the right ICA and a turbulence artifact within it

ventricular dilatation and meningeal inflammation. Microscopic analysis showed a polymorphonuclear neutrophilic infiltrate and necrotic debris. Fungal hyphae were detected using Periodic Acid-Schiff (PAS) and Gomori–Grocott stains (Figs. 5, 6). The presence of wide and irregular, thin-walled aseptate hyphae with right-angle branching was consistent with a diagnosis of mucormycosis [1]. Fungal hyphae also invaded vessel walls and were found in intravascular thrombi (Fig. 5).

Discussion

Mucormycosis is a rare filamentous fungal infection with an incidence of 0.9–1.7 cases per million per year [1, 7] and a prevalence at autopsy of 1–5 for 10,000 cases [1].

Rhino-orbital-cerebral form of the disease counts for 40–50 % of cases [1, 3] with diabetes being the most common predisposing factor [3, 4, 8]. Other underlying conditions include solid organ or bone marrow transplantation, intravenous drug use, malignant hemopathies, high-dose corticosteroid therapy, induced immunosuppression, iron overload and deferoxamine therapy, cirrhosis, congenital cardiopathy, malnutrition, and chronic alcohol addiction [3, 9]. Rhinocerebral mucormycotic infection starts with inhalation of airborne spores [2, 9, 13]. In immunocompetent host, complement activation, chemotaxis, phagocytosis and production of oxidative metabolites by macrophages and neutrophils prevent spore germination and hyphal invasion [2, 4, 5, 13, 14]. Polymorphonuclear function can be compromised in hyperglycemic and acidotic environment [1, 8, 13]. Iron also plays a role as a growth factor in mucormycotic infection pathogenesis. The hallmark of Mucorales infection is its vascular tropism: pregerminated sporangiospores of *R. oryzae* can adhere to subendothelial matrix proteins and then be phagocyted by endothelial cells. Especially, *R. oryzae* synthesizes an alkaline protease allowing dissection of the internal elastic lamina from the media by cleaving elastin.

Clinical features of rhinocerebral mucormycosis usually consist in initial, usually ethmoïd or maxillary sinusitis [15], soft tissue swelling, and periorbital cellulitis. Neurological manifestations include headache, trigeminal involvement, blurred vision to visual loss, ophthalmoplegia and peripheral facial nerve palsy. Specific syndromes such as orbital apex, superior orbital fissure or cavernous sinus syndromes, according to the infection's way of extension may also occur. Arterial intracranial mucorthrombosis eventually complicated by septic strokes, mucormycotic vasculitis and cavernous sinus thrombosis are also

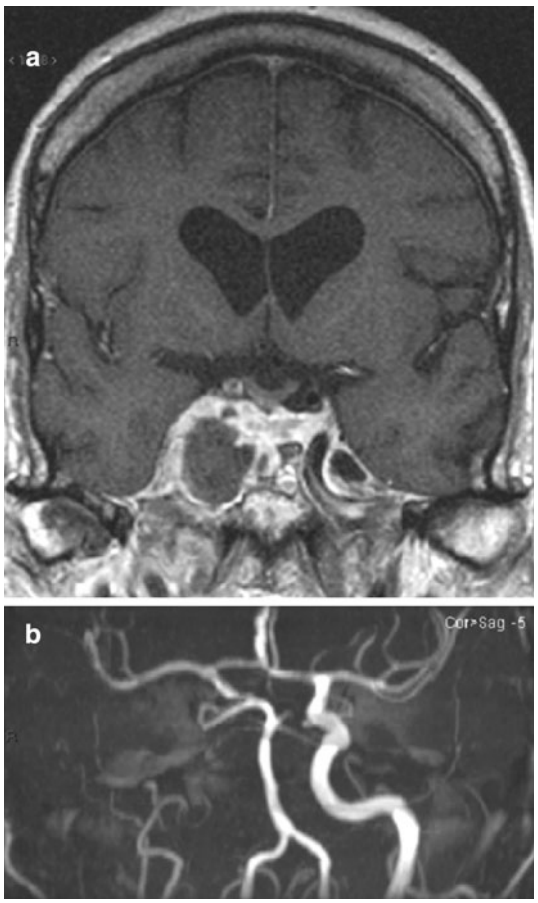

Fig. 3 MR work-up in May 2007: **a** contrast-enhanced coronal T1-weighted image showing mass effect of the right cavernous sinus with enhanced peripheral rim surrounding central unenhanced fresh thrombus. **b** Frontal reformat of TOF angiogram demonstrating absence of flow within both extra-cranial and intra-cavernous segments of right ICA. Flow within distal segment of ICA and middle cerebral artery is preserved by collateral vicariance through communicating arteries resulting in the absence of acute parenchymal ischemic lesion, even on diffusion-weighted images (not shown)

described. Other central nervous system manifestations such as cerebral abscess, mycotic aneurysms with subarachnoidal hemorrhage, meningitis, cognitive impairment, convulsion or chronic hydrocephalus are reported [1, 2, 4, 6, 8, 11, 13–17].

In our case, the right facial pain may have been caused by initial sphenoid sinusopathy and trigeminal nerve irritation. The sixth nerve was thereafter involved completing a partial progressive right-sided cavernous sinus syndrome. The mechanism of cranial nerve involvement can be compression leading to nerve ischemia, neural vasculitis or direct perineural invasion with fungal neuritis [16, 17].

Initial CSF findings are variable and unspecific: there might be a slightly increased opening pressure, a mild pleocytosis (often with neutrophilic predominance), normal or slightly elevated proteins and uncommonly a low glucose content. All these CSF changes were found in our patient [18, 19]. Later, delayed appearance of CSF-specific oligoclonal IgG bands revealed the progression of the intracerebral infection with a intrathecal inflammatory and immune response.

Mucormycosis is usually a fulminant infection evolving over a few days; but, authors reported a chronic course [11, 17, 20, 21] defined by the presence of symptoms and signs for more than 4 weeks.

Although mucormycosis has been reported rarely in immunocompetent individuals, many reports are available in the literature [10–12, 15]. In a review of 929 cases, Roden et al. [10] found that 19 % of zygomycotic infection could occur in previously healthy subjects. About half of these patients had history of brain trauma or prior local surgery. Nasal or sinus procedure and chronic sinusitis can be retained as predisposing factors [11, 12, 15].

Our patient exhibited several unusual features:

1. onset of the infection in the sphenoid sinus, associated with a more indolent and progressive course of the disease [17]
2. an early cavernous sinus syndrome, likely due to a persistent, post-surgical bone disruption linking the sphenoid and cavernous sinuses
3. a mucormycotic aneurysm and thrombosis of the right ICA, without periorbital cellulitis or orbital apex syndrome [6, 18, 19, 22]
4. a long-lasting course of 10 months in the absence of diabetes or immunocompromised condition (a substitutive treatment by low dose of hydrocortisone is not susceptible to induce an immune depression, and our patient indeed did not present signs or symptoms of immune deficiency).

ICA mucormycotic aneurysm remains exceedingly rare [23–25]. Alvernia et al. [26] reported what they thought to be the first case of mucormycotic ICA pseudoaneurysm, successfully treated by endovascular embolization together with surgical debridement and antifungal therapy. Their patient presented, like ours, an initial cavernous sinus syndrome without initial orbital cellulitis. Hashemzadeh et al. [23] reported a case of common carotid artery pseudoaneurysm and reviewed eight cases of mucormycotic aneurysm between 1981 and 2007, none of them involving the ICA. Mielke et al. [25] in an older review (1950–1980) found two cases of "phycomycotic" ICA aneurysm, both with a well-recognized predisposing factor. Our case could thus be the fourth with a mucormycotic ICA aneurysm, and the second occurring after transsphenoidal surgery. Two cases of fungal aneurysms after a prior transsphenoidal surgery have been reported. The first one [25] presented both mycotic internal carotid and basilar aneurysms 6 months after a transsphenoidal surgery for a somatotropic macroadenoma invading the cavernous sinus.

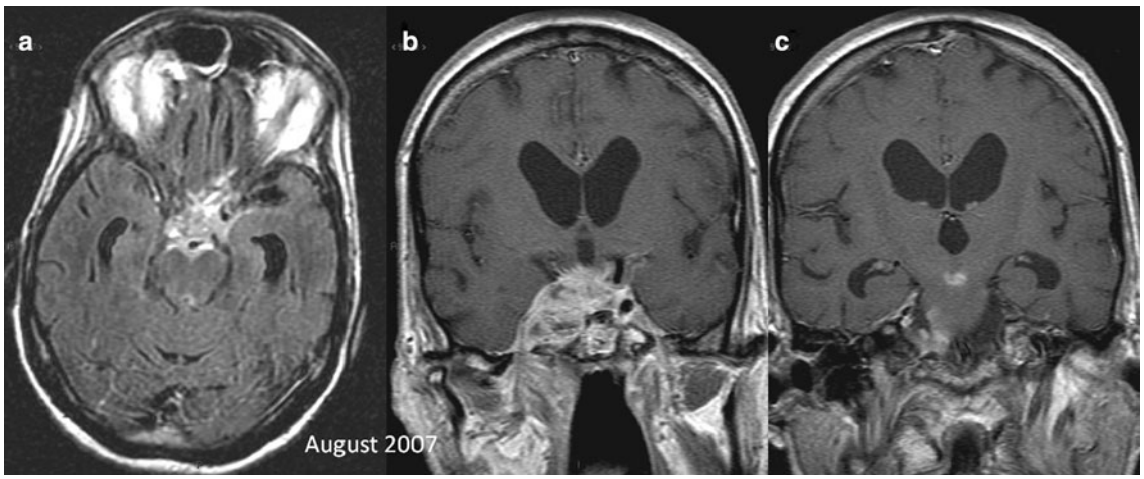

Fig. 4 MR work-up in August 2007: post-contrast axial transverse (**a**) and coronal T1-weighted images (**b**) showing progression of hyperintense and enhancing mass of the skull base with meningeal involvement and ventricular enlargement. **c** Axial transverse diffusion-weighted image showing acute ischemic focus in the right thalamo-mesencephalic junction

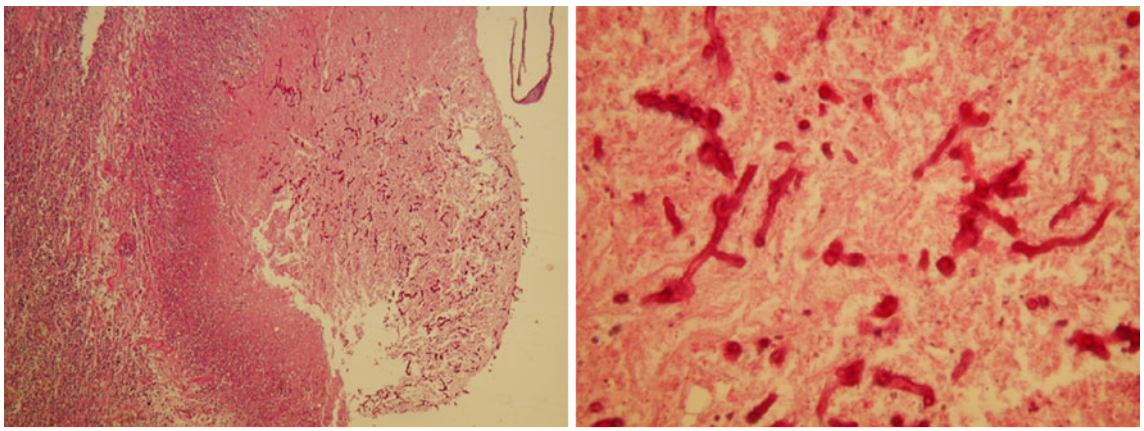

Fig. 5 Periodic Acid-Schiff stain: intravascular mucorthrombus and necrotic debris in the vessel wall. Right angle branching, irregular, thin-walled hyphae with vacuolar aspect on transversal sections

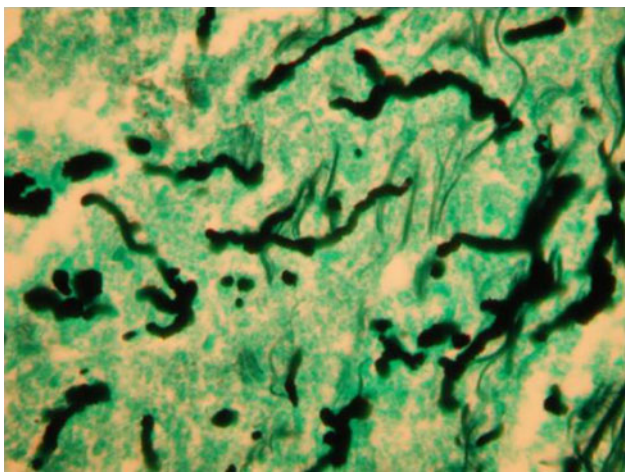

Fig. 6 Gomori-Grocott stain: fungal hyphae, irregular, twisted, with variations in diameter

Their patient died of basal subarachnoid hemorrhage due to the ruptured basilar aneurysm. There was histological evidence of chronic meningitis containing fungal hyphae. The second case [27] was that of a patient with bilateral "mirror" mucormycotic aneurysms of anterior cerebral arteries revealed by fever, meningeal signs and meningitis 1 month after transsphenoidal surgery for a pituitary macroadenoma.

In conclusion, delayed neurological signs and symptoms after transsphenoidal surgery should be promptly managed and the possibility of a fungal infection kept in mind. In our case, previous surgery and radiotherapy together with macroadenoma residues may have resulted in local fragility and hypoxic environment predisposing our patient to this rare fungal infection, as it has been hypothesized for diabetic patients [10]. Anyway, we have no definite explanation for the long delay between surgery and clinical

infection. Inhalation and infection through the prior surgical pathway could be considered. Surgical debridement or biopsy is warranted to allow firm histological diagnosis and to initiate appropriate anti-fungal therapy as early as possible.

Conflict of interest None.

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