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Case Study and Literature Review: Pituitary Mucormycosis Diagnosed after Macroadenoma Resection

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Abstract

Mucormycosis is a potentially fatal fungal disease that can affect immunocompetent as well as immunocompromised patients. This infection typically occurs in patients with diabetic ketoacidosis and patients in treatment with chemotherapy for hematologic neoplasia among other conditions. Diagnosis of mucormycosis is supported by clinical manifestations as well as mycological and histopathological analysis. High rates of morbidity have been linked to the delay of diagnosis, reinforcing the need for early diagnosis. The present case report is about a patient diagnosed with mucormycosis based on anatomopathological analysis of pituitary's material after macroadenoma resection.

Keywords: Mucormycosis; Diagnosis; Treatment; Pituitary macroadenoma; Fungi infections

Abbrevations: GI: Gastrointestinal; CT: Computed Tomography; TSH: Thyroid Stimulating Hormone; FSH: Follicle Stimulating Hormone; LH: Luteinizing Hormone; CBC: Complete Blood Cell Count; CNS: Central Nervous System; CSF: Cerebro Spinal Fluid; BAL: Bronchoalveolar Lavage; qPCR: Quantitative Polymerase Chain Reaction; MRI: Magnetic Resonance Imaging.

Introduction

Mucormycosis, previously called zygomycosis, refers to several different diseases caused by infection with fungi in the order Mucorales. Rhizopus species are the most common causative organisms. In descending order, the other genera with mucormycosis-causing species include *Mucor, Cunninghamella, Apophysomyces, Lichtheimia (formerly Absidia), Saksenaea, Rhizomucor*, and other species. Most mucormycosis infections are life-threatening, and risk factors such as diabetic ketoacidosis and neutropenia are present in most cases. Severe infection of the facial sinuses, which may extend into the brain, is the most common presentation. Pulmonary, cutaneous, and gastrointestinal (GI) infections are also recognized. Successful mucormycosis treatment requires correction of the underlying risk factor(s), antifungal therapy (traditionally with a polyene), and aggressive surgery [1,2]. We here report a case of a diabetic male patient with pituitary mucormycosis identified after macroadenoma resection.

Case Report

J.J.N., a 55-years-old male, with type-2 diabetes and hypertension, currently uses gliclazide 30 mg and losartan 50 mg once a day. He was admitted to Hospital Universitário Evangélico Curitiba PR Brazil (HUEC) by the

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neurosurgery department and had a history of 3 days of fever (maximum temperature of 102.2^{0}F), decrease of general health status and hyporexia. There were no complaints of cough, odynophagia, otalgia, no alterations of genitourinary and gastrointestinal habitus. At admission patients presented hypotension (70/40 mmHg) with partial response after volemic reposition.

Patient's past history reported 15 days of intermittent migraine on right frontal lobe that was treated by administration of commonly used analgesic drugs. There were no complaints of nauseas or vomits associated with the presence of intermittent diplopia, mainly detected after horizontal movement of the eye to the left, which started 7 days after the primary symptoms, that was recovered progressively on the following days. Computed tomography (CT) of the head detected an increased diameter of sella turcica and sella turcica's MRI demonstrated a large heterogenic expansive lesion centered in the sellar region that also accomplished a large area of sphenoid sinuses that apparently dislocated the pituitary gland posterior-superior suggesting a hemorrhagic pituitary macroadenoma with extension into sphenoid sinus (Figure 1). Patient was then submitted to a microsurgery for resection of the expansive sellar lesion with intralesional hemorrhage and compression of optic chiasma. After surgery, patient developed central diabetes insipidus that was reverted with desmopressin used daily and pan-hypopituitarism (TSH 0,04; FSH 0,6; LH 0,25, PRL < 0,6) – measured while hospitalization at HUEC that showed signs of improvement after administration of hydrocortisone IV and levotiroxine.

Anatomo pathological definitive report of pituitary chirurgical piece showed hyalohyphomycosis, suggesting mucormycosis (Figure 1&2) and skull CT evidenced the presence of material on maxillary sinus (on the right), pedunculate filled with liquid (Figure 3), material at sphenoidal sinus, ethmoid cells and frontal sinus. Patient was then submitted to a biopsy of maxillary sinus by the otorhinolaryngology team that confirmed mucormycosis. During the period of hospitalization, patient presented glycemic lability, hypoglycemic periods that needed high doses of insulin and hypoglycemic periods that improved after disruption of insulin therapy. When patient was released from HUEC he was hemodynamic stable, controlled blood glucose and no signs of fever. On December 7, 2017, the patient completed the treatment of mucormycosis at Day Hospital after receiving 105 doses of liposomal amphotericin B. Currently patient reports feeling well using somatropin 11U subcutaneously at night, hydrocortisone 10mg 2x / day, levothyroxine 75mcg, metformin 500mg after dinner and Nebido 1 ampoule intramuscularly every 3 months due to pan-hypopituitarism. Follow-up continues at the endocrinology and otorhinolaryngology department of HUEC.

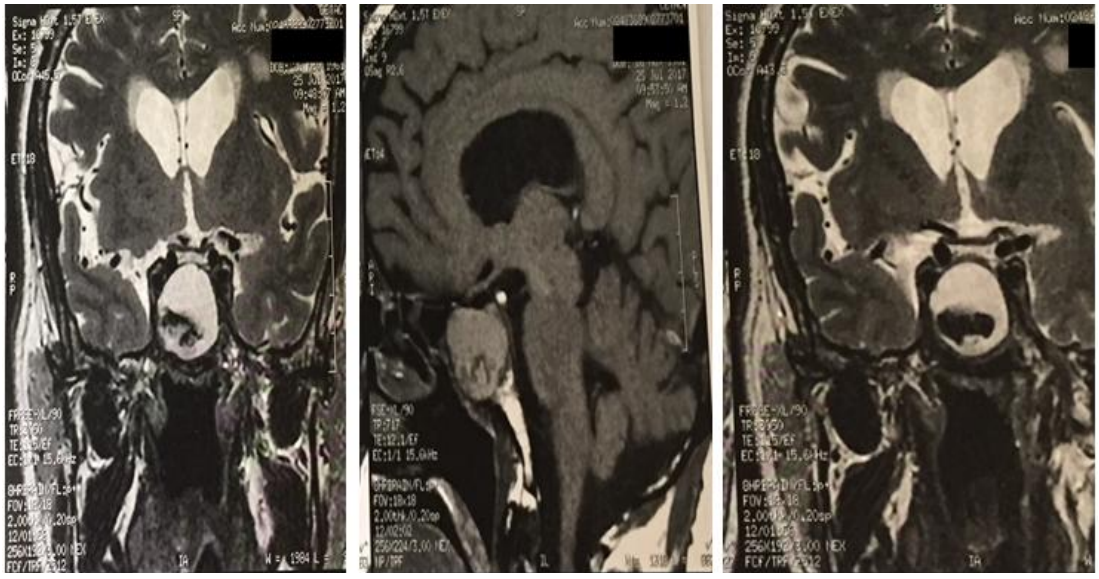

Figure 1: Heterogeneous expansive lesion at sellar region.

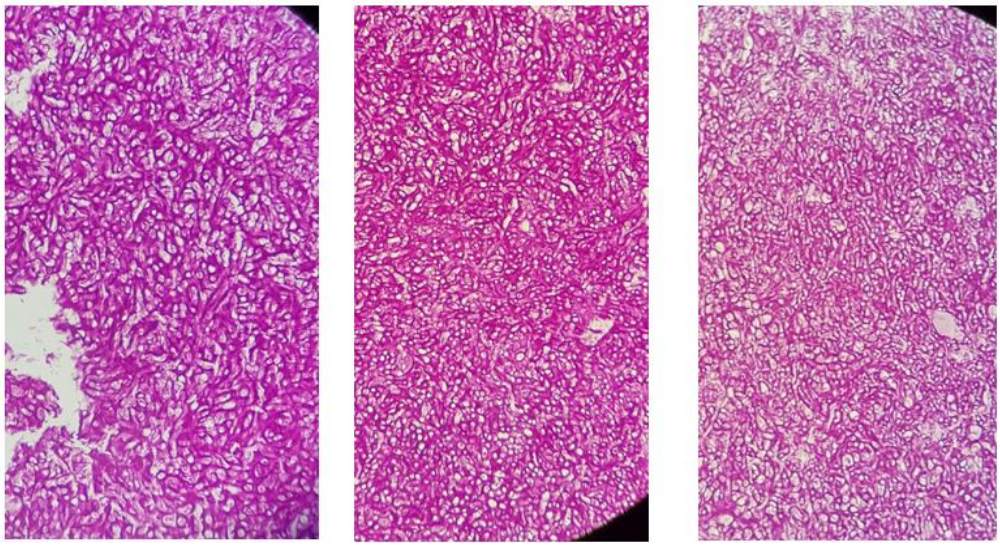

Figure 2: Hyalohyphomycosis on pituitary chirurgical piece.

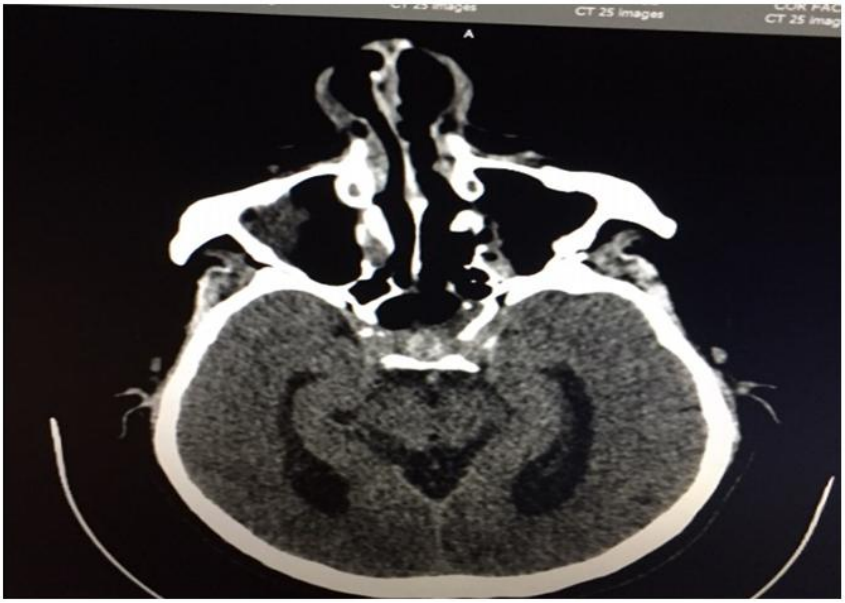

Figure 3: Material at maxillary sinus on the right with liquid level.

Discussion

Mucormycosis is a life-threatening infection caused by fungi of the order *Mucorales*. Recent reclassification has abolished the order Zygomycetes and placed the order *Mucorales* in the subphylum *Mucormycotina* [3]. This rare and highly invasive infection occurs preferentially in immunosuppressed individuals [4]. Rhino-orbital-cerebral and pulmonary infections are the most common syndromes caused by these fungi [1]. The most common etiological agent is *Rhizopusoryzae*, that is responsible for 60% of all forms of mucormycosis, along with *Mucor* and Absidia [5]. *Cunninghamella*, *Absidia*, *Saksenaea*, and *Apophysomyces*are genera that are less commonly implicated in infection [1].

Rhizopus organisms have an enzyme, ketone reductase, which allows them to thrive in high glucose, acidic conditions. Serum from healthy individuals inhibits growth of *Rhizopus*, whereas serum from individuals in diabetic ketoacidosis stimulates growth. Rhino-orbital-cerebral and pulmonary mucormycosis are acquired by the inhalation of spores. In healthy individuals, cilia transport these spores to the pharynx and they are cleared through the gastrointestinal tract. In susceptible individuals, infection usually begins in the nasal turbinates or the alveoli. The agents of mucormycosis are angioinvasive; thus, infarction of infected tissues is a hallmark of invasive disease [1].

Mucormycosis typically occurs in patients with diabetic ketoacidosis or poorly controlled diabetes, patients receiving chemotherapy by lymphoproliferative disease or another neoplasia, or under corticoid therapy, patients that have received organ or hematopoietic stem cell transplant and even in patients without apparent predisposed factors [6]. Other underlying risk factors include AIDS, trauma, treatment with deferoxamine, use of intravenous drugs and malnutrition [1]. The number of cases is increasing constantly, mostly dependent on the prevalence of the risk factors cited above as well as by the increased lifespan of those on immunosuppress therapy and general population [6]. A review of 929 cases of mucormycosis that were reported between 1940 and 2003 noted that diabetes mellitus was the most common risk factor, found in 36% of cases, followed by hematologic malignancies (17%) and solid organ or hematopoietic cell transplantation (12%). In some patients, mucormycosis was the diabetes-defining illness. In a later study of 101 patients diagnosed with mucormycosis between 2005 and 2007 in France, hematologic malignancy was the most common risk factor, occurring in 50% of patients, followed by diabetes in 23% and trauma in 18% of cases [1].

The number of reported cases of mucormycosis in diabetic patients in the United States has declined since the 1990s, a trend that has not been noted in France or in developing countries. One hypothesis that has been suggested to explain the decline in the United States is the widespread use of statins, which have inhibitory activity in vitro against a wide range of the agents of mucormycosis [1]. The incidence of this infection in Brazil is unknown; there are only a few case studies that were published; however there is a trend for predominance of cases on the North and North West regions of Brazil [7].

The infection usually presents as acute sinusitis with fever, nasal congestion, purulent nasal discharge, headache, and sinus pain. All of the sinuses become involved, and spread to contiguous structures, such as the palate, orbit, and brain, usually progresses rapidly. However, this disease can be also manifested in conjunction with fever, lethargy, headaches, retro-orbital pain, abrupt vision loss, proptosis, periorbital cellulitis, epistaxis and convulsions [1,7].

The trademarks of spread beyond the sinuses are tissue necrosis of the palate resulting in palatal eschars, destruction of the turbinates, perinasal swelling, and erythema and cyanosis of the facial skin overlying the involved sinuses and/or orbit [3]. Spread from the sphenoid sinuses to the adjacent cavernous sinus can result in cranial nerve palsies, thrombosis of the sinus, and involvement of the carotid artery. Hematogenous spread to other organs is rare unless the patient has an underlying hematologic malignancy with neutropenia [1]. Central nervous system (CNS) mucormycosis usually arises from an adjacent paranasal sinus infection. Yet, there have been more than 30 cases of isolated CNS mucormycosis described in the literature. Infection is thought to result from seeding of the brain during an episode of fungemia, analogous to renal involvement. Over two-thirds of the patients with isolated CNS mucormycosis have been intravenous drug users who presumably have injected material contaminated with fungi directly into the bloodstream. Some of the patients with isolated CNS mucormycosis have had HIV infection in addition to drug use [1].

The fact that mucormycosis is a rare human infection reflects the ineffectiveness of early diagnosis of this disease. The first suspect evoking sign for rhino-orbital-cerebral infection is periorbital edema with orbital pain or the presence of erythema and painful palate edema. Its progression to cutaneous or mucus necrosis happens within hours, which can be preceded or not by mucopurulent or bloody rhinorrhea. Subsequently there is the association of fever of variable intensity, migraines and signs of toxemia and alterations of general health status. This might be the best timing for presumptive diagnostic that can result on better prognostic [6].

Clinical diagnosis of patients with suspected rhino-cerebral mucormycosis should consider the following: orbital cellulitis, thrombosis of cavernous sinus, fast growing orbit tumor, *aspergillosis*, infection by *llescheria boydii (*the asexual form*: Scedosporiumapiospermum) (psedallescheriasis)* and *Pseudad Fusarium infection*. Aspergillosis, pseudallescheriasis, fusariosis, nocardiosis, Wegner's granulomatosis, pulmonary emboly and malignancy also should be considered when diagnosing a patient with suspected pulmonary mucormycosis. Regarding cutaneous disease, ecthyma gangrenosum

associated to pseudomonas and anthrax infections should be considered. Considerations about gastrointestinal disease should include intestinal obstruction and ilocecal tuberculosis [2]. Clinical suspicious of mucormycosis is an indicative for initiating treatment. Patients with suspected rhinocerebral disease should undergo emergent computed tomography (CT) imaging of the paranasal sinuses and an endoscopic examination of their nasal passages with biopsies of any suggestive lesions. The diagnosis of mucormycosis is established by obtaining a biopsy specimen of the involved tissue, and frozen tissue samples should be immediately evaluated for signs of infection. Tissue should also be sent for routine pathology examination and cultures. Swabs of tissue or discharge are unreliable [2]. For pulmonary disease, a bronchoalveolar lavage (BAL), biopsy, or both may assist in the diagnosis. For cutaneous disease, a skin biopsy for pathology and culture should be obtained [2].

A complete blood cell count (CBC) should be obtained to assess for neutropenia. A chemistry panel that includes blood glucose, bicarbonate, and electrolytes is useful to monitor homeostasis and direct correction of acidosis. Iron studies may be indicated to assess the presence of iron overload as shown by high ferritin levels and a low total iron-binding capacity [2]. In cases of central nervous system (CNS) involvement, cerebrospinal fluid (CSF) findings may include elevated protein levels and a modest mononuclear pleocytosis. CSF cultures are typically sterile. A CT scan should precede a lumbar puncture to assess for evidence of elevated intracranial pressure, which could lead to herniation [2].

Blood cultures can be obtained; however, they are usually negative despite the angioinvasive nature of the organism. Blood cultures may be useful to detect bacteremia as an independent predictor of 28-day mortality. There are no specific biomarkers to identify mucormycosis. Bronchoalveolar lavage (BAL) of fluid culture has a low yield, with sensitivity of 20-50%. Antigen tests (beta-D-glucan or galactomannan) are not useful for detecting this infection [2]. The use of quantitative polymerase chain reaction (qPCR) for detection of circulating DNA from common Mucorales species (*Lichtheimia species, Rhizomucor species,* and *Mucor/Rhizopus* species) while not yet commercially available, has been described and appears promising for the early diagnosis of mucormycosis in high-risk patients. In a retrospective analysis of 44 cases, qPCR identification was fully concordant with that of culture. Assay positivity was observed at an average of 9 days, at least 2 days prior to positive imaging findings. Development of PCR negativity after treatment was associated with higher survival rates (48% vs 4%), suggesting that this modality could eventually be used for treatment monitoring [2].

Imaging should be used to investigate areas of suspected mucormycosis. Because of subclinical disease may be present, a detailed history and physical examination are recommended in addition to imaging (CT) of the brain, sinuses, chest, and abdomen [2]. In relation to rhinocerebral infections, plain films may show sinus involvement with mucosal thickening, air-fluid levels, and/or bony erosions [2]. Head and facial CT imaging should be used as the initial investigation in rhinocerebral infections. CT scans may show sinusitis of the ethmoid and sphenoid sinuses, as well as orbital and intracranial extension. As the disease progresses, bony erosion may occur and the infection may spread into the brain or orbits. Furthermore, because mucormycosis organisms have a predilection for vascular involvement, thromboses of the cavernous sinus or internal carotid artery may occur. All of the areas of involvement must be understood in order to plan the extent of surgical debridement. Magnetic resonance imaging (MRI) of the facial sinuses and brain is superior to a CT scan in assessing the degree of tissue invasion and need for ongoing surgery [2].

CT scanning or MRI of the central nervous system may reveal abscesses (especially in the setting of intravenous drug use) or extension of rhinocerebral disease into the brain. Cavernous and, less commonly, sagittal sinus thrombosis may also be seen [2].

Treatment

Treatment of mucormycosis involves a combination of surgical debridement of involved tissues and antifungal therapy. Exclusion of predisposing factors for infection, such as hyperglycemia, metabolic acidosis, deferoxamine administration, and neutropenia, is also fundamental [1]. The drug of choice for initial therapy of mucormycosis is a lipid formulation of amphotericin B. Posaconazol or isavuconazole can be used for oral step-down therapy for patients who have responded to a lipid formulation of amphotericin B. Posaconazol or isavuconazole can be also used as salvage therapy for patients who do not respond to or cannot tolerate amphotericin B; for salvage therapy, the decision to use intravenous or oral posaconazole or isavuconazole depends on how ill the patient is, whether an initial course of amphotericin B was able to be administered, and whether the patient has a functioning gastrointestinal (GI) tract. Aggressive surgical debridement of involved tissues should be undertaken as soon as the diagnosis of any form of mucormycosis is suspected. In the case of rhinocerebral infection, debridement to remove all necrotic tissue will often be

disfiguring, requiring removal of the palate, nasal cartilage, and the orbit [1].

In one study, amphotericin B lipid complex resulted in a 71% success rate as salvage therapy for mucormycosis. Furthermore, treatment with liposomal amphotericin B (LAmB) was associated with 67% survival rate (16 of 24 patients) compared with 39% survival (24 of 62 patients) with amphotericin B deoxycholate (P = 0.2) among patients with cancer who experienced mucormycosis [3]. The usual starting dose is 5 mg/kg daily of liposomal amphotericin B or amphotericin B lipid complex, and many clinicians will increase the dose up as high as 10 mg/kg daily in an attempt to control this infection [1]. The optimum dosages for treatment of mucormycosis are not known for any antifungal agent [3].

Overall mortality from rhino-orbital-cerebral mucormycosis ranges from 25 to 62 percent, with the best prognosis in patients with infection confined to the sinuses. The prognosis is especially poor for patients with brain, cavernous sinus, or carotid involvement, although some patients with these complications have been cured of the infection. The outcome in patients with pulmonary mucormycosis is worse than for patients with rhino-orbital-cerebral involvement, with mortality rates as high as 87% [1].

Conclusion

Being a delayed treatment an independent factor for poor outcome, a successful result is base on a high level of clinical suspect of the disease and its associated risk factors, thus making it possible to obtain early diagnosis and appropriate combine surgical-medical management.

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