Annals of Medicine and Surgery 6 (2016) 87–91

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.annalsjournal.com

Case report

Chronic rhino-orbito-cerebral mucormycosis: A case report and review of the literature

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HIGHLIGHTS

- We describe the case of a chronic rhino-orbito-cerebral mucormycosis.
- Chronic mucormycosis has low rate of frequency and is difficult to diagnose.
- A quarter of chronic rhino-orbito-cerebral mucormycosis cases are in immunocompetents.
- Surgical debridement is the corner stone of mucormycosis treatment.
- Survival rate in chronic mucormycosis cases (83%) is higher than acute cases (10–35%).

ARTICLE INFO

Article history:
Received 28 November 2015
Received in revised form
3 February 2016
Accepted 3 February 2016

Keywords:
Chronic mucormicosis
Rhinocerebral mucormicosis
Mucoraceae
Rhino-orbito-cerebral
Amphotericin

ABSTRACT

Mucormycosis is a life-threatening disease, were rhinocerebral infection is most commonly seen in the clinical setting. Chronic mucormycosis is a rare presentation that exhibits a challenging diagnosis. We describe the case of a 47 year old diabetic man with complains of left zygomatic arch swelling of 3 months evolution. He had received previous antibiotic treatment without improvement. Biopsy of maxillary sinus revealed the presence of non-septated, 90° angle branched hyphae compatible with zygomicetes. The patient was treated with surgical debridement and amphotericin B until there was no evidence of fungi in the tissue by biopsy. We reviewed chronic rhino-orbito-cerebral mucormycosis from 1964–2014 and 22 cases were found, being this the second case of chronic mucormycosis reported in Mexico. A quarter of the cases were seen in immunocompetent hosts. As only 20% of the causal agent can be isolated by culture, the diagnosis is mainly made by biopsy. Besides treatment with amphotericin B, posaconazole as alternative, and control of the underlying comorbidities, surgical debridement represents the corner stone therapy. We recommend at least 36 month follow-up, due to the 13% risk of recurrence. A chronic presentation has a general survival rate of approximately 83%.

1. Introduction

Mucormycosis is an invasive infection caused by filamentous fungi belonging to the order Mucorales with rhinocerebral infection being the most common clinical presentation [1]. According to time of evolution the infection can be acute or chronic, with the latter having a low frequency (5.6% of rhinocerebral mucormycosis cases). [1,2].

We present a case of chronic mucormycosis rhinocerebral

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http://dx.doi.org/10.1016/j.amsu.2016.02.003

infection in a 47yo male and a review of literature. To our knowledge, this is the second case of chronic mucormycosis reported in Mexico [3].

2. Presentation of case

A 47-year-old male was evaluated because of a 3-month history of paresthesia, pain and swelling in the left zygomatic bone. He had previously attended the clinic on several occasions where he was diagnosed with type 2 diabetes mellitus (DM2) and sinusitis, receiving unspecified antibiotic treatment. Subsequently, he came to our institution with swelling on the left half of his face, and erythema and pain on palpation. A CT scan of his paranasal sinus (Fig. 1) revealed an erosion of the malar bone and the lateral orbit wall, edema of preseptal tissue without involvement of intraorbital structures. The patient was subjected to several biochemical tests and presented a white blood cell count of 10.3 Kc/mL, platelets 27 Kc/mL, BUN 10 mg/dL, serum creatinine 0.8 mg/dL, and a serum glucose level of 239 mg/dL. Biopsies were obtained during a Cadwell-Luc procedure. Microscopically the tissue of the maxillary sinus revealed the presence of non-septated 90° angle branching hyphae compatible with zygomycetes (Figs. 2 and 3). For this reason debridement with a modified midfacial degloving approach of the left maxillary mucosa, the anterior and lateral maxillary walls, and the adjacent area of the malar bone was performed; the floor of the orbit was preserved. Biopsy revealed presence of hyphae zygomycetes, with some areas of acute infiltrate, granulomatous chronic infiltration and regions with evident angioinvasion.

In addition, Ziel-Nielsen and periodic acid-Schiff stains were carried out and both were negative. Amphotericin B deoxycholate therapy was administered with the patient receiving a total dose of 2575 mg in 26 days. The patient presented tubulointerstitial nephritis (Serum Creat 2.5 mg/dl) and was assessed by a nephrologist. In consensus with the patient, it was decided to continue the same therapy (because of a lack of posaconazole in our setting) until evidence of mycotic tissue was absent, achieved by left type III antrostomy and biopsy of surgical bed tissue. During evaluation, a tissue culture was done but there was no growth of fungi or mycobacteria. At four months follow-up, there has been no evidence of recurrence and the patient is currently asymptomatic.

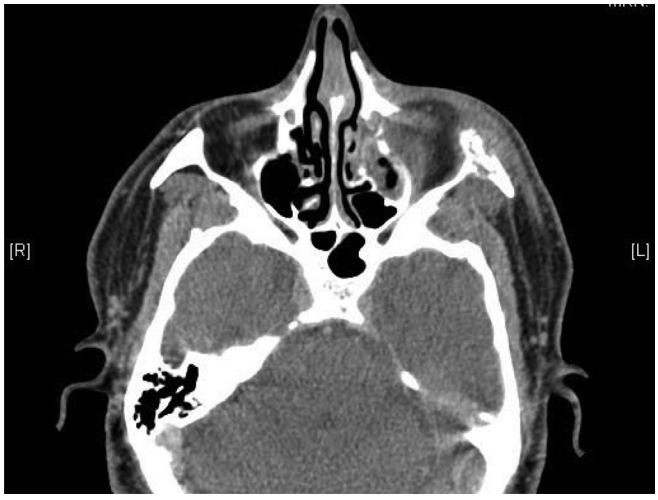

Fig. 1. Bone erosion of left malar bone is identified in the computed tomography scan with extension to the lateral orbital rim, zygomatic arch and ipsilateral palate, associated with edema of preseptal soft tissue, the presence of small subperiosteal collection upper outer margin, with occupation of the maxillary sinus, without enhancement after contrast administration.

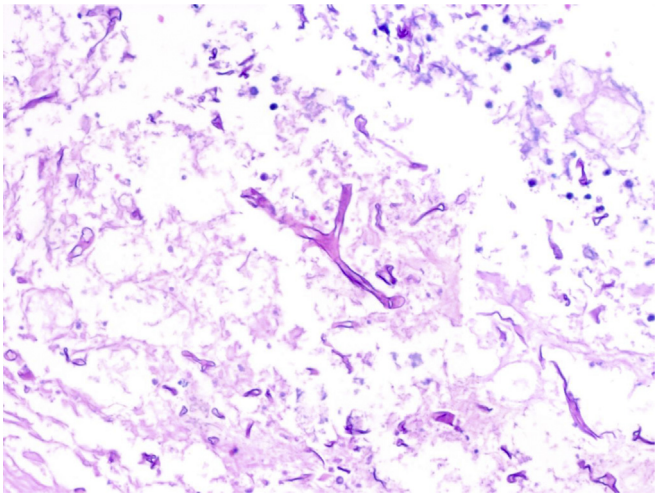

Fig. 2. Irregular, thick, non-septate and fragmented hyphae between the necrotic tissue. PAS 40x.

3. Discussion

We searched PubMed database from 1964 to 2014 for all available articles in the English language related to rhino-orbital-cerebral chronic infections caused by fungi of the order Mucorales and found 22 cases. In Table 1 we summarize the characteristics of the reported chronic rhino-orbito-cerebral cases.

Mucormycosis is an opportunistic infection that affects immunosuppressed patients with a decreased ability to phagocytize. [1,4] It also has been described in immunocompetent patients with an incidence of 4–19%. [5–8] The infection originates in the upper airway by inhalation of spores. [1,9] Its pathogenic form was recognized in 181510, with the first case of mucormycosis in humans being described by Palauf in 1855.11,12 The first documented case of chronic mucormycosis was described by Vignale in 1964.2.

The infection can present in locations such as the skin, lung, gastrointestinal tract, and as a rhino-orbito-cerebral infection, this being the most common. [4,11,12] In our review we found that 26% of chronic rhino-orbito-cerebral mucormycosis occurred in immunocompetent patients. Initial clinical manifestations include

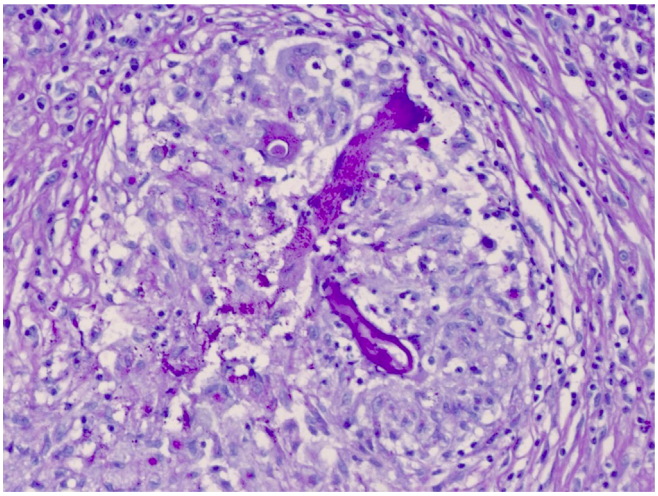

Fig. 3. Granuloma image consisting of lymphocytes and epithelioid cells, highlighting its central portion a non septate hyphae. PAS 40x.

nasal congestion and local symptoms such as eye pain or maxillary sinus [4,11]. Ophthalmic symptoms such as proptosis or ptosis, ophthalmoplegia, vision loss and pain in the retrobulbar region were found in 72% of patients [2].

Hematogenous dissemination occurs due to the angioinvasiveness of the fungi. [1,10,12,14] In fact, vascular tropism is the hallmark of Mucorales; for example, pre germinated sporangiospores of *Rhizopus oryzae* can adhere to subendothelial matrix proteins and then be phagocyted [8], resulting in vascular thrombosis, infarction and necrosis of surrounding tissues. [1,10,12,14] Cavernous sinus and internal carotid artery thrombosis are more frequent in chronic presentation [11]. Factors associated with angioinvasiveness are defects in phagocytic function, both quantitative and qualitative and increase in iron and glucose serum concentrations, as seen in patients with diabetic ketoacidosis, hematological neoplasms, chemotherapy-induced neutropenia, and use of deferoxamine, becoming apparent that Mucorales rarely infects patients with granulomatous diseases. [1,4].

There is no exact definition of chronicity, which can vary from weeks to months [1]. Classically, it is defined by symptoms that last for more than 4 weeks. [2,13] In the reported chronic cases, the average was 7 months. In comparison, acute infection presents

Table 1
Characteristics of patients with chronic rhino-orbito-cerebral mucormycosis, treatment and outcome.

Study	Patient	Carotid artery thrombosis	Cavernous sinus thrombosis	Isolated microorganism	Treatment	Duration of symptoms	Duration of treatment	Outcome
Vignale et al [19] 1964 Uruguay	F 39 yo Immunocompetent	Unspecified	Unspecified	*Mucor ramosissimus*	Surg Griseofulvina 1 g/d per 30 d AmB 1 g	24 y	20 d	No relapse (unspecified time)
Helderman et al [18] 1974 USA	M 55 yo DM2	Yes	Unspecified	None	Surg AmB 1 g	1 m	6 wk	Without relapse at 10 m
Ferstenfeld JE et al. [10] 1977 USA	F 61 yo DKA	Yes	No	None	Surg AmB 371 mg	2 m	Unspecified	Without relapse at 48 m
	M 36 yo DKA	Yes	No	*Rhizopus nigrans*	Surg AmB 2.2gr	14 d	22 d	Relapse at 36 m
Finn DG et al [11] 1982 USA	M 82 yo DM3	Unspecified	Unspecified	None	Surg AmB	2 wk	33 d	Relapse at 22 wk
	M 68 yo Lymphoma/DKA	Unspecified	Unspecified	None	Surg AmB 3gr	2 wk	Unspecified	Without relapse at 13 m
McDevitt GR et al [13] 1989 USA	M 45 yo DM2	Yes	Yes	None	Surg AmB	1 m	2wk	Unspecified
Hauman CHJ et al [8] 1989 South Africa	F 10 mo Denutrition/ dehydration	Yes	Yes	None	AmB/Ketoconazole[a]	6 m	5 wk	Died
	F 14 yo Denutrition/ dehydration	Unspecified	Unspecified	None	Surg Ketoconazole	5 y	Unspecified	Lost of follow-up
Dooley DP et al [12] 1992 USA	M 45 yo DM2	Yes	Yes	None	Surg AmB 2gr	7 wk	6 wk	Without relapse at 48 m
Tyson JC et al [15] 1992 USA	F 26 yo Immunocompetent	No	No	*Rhizopus* spp.	Surg AmB 680 mg	5 y	1 m (then 20 mg/m unspecified time)	Without relapse at 36 m
Ericsson M et al [16] 1993 Sweden	F 48 yo Alcohol abuse DM2	Yes	Yes	None	Surg AmB 20 g (liposomal)	3 m	8 m	Without relapse at 18 m
Goodnight J et al [17] 1993 USA	M 72 yo Immunocompetent	No	No	None	Surg[b]	5 y	–	Without relapse at 7 m
Handa et al [9] 1996 India	M 55 yo immunocompetent	No	Yes	None	Surg AmB 575 mg	1 y	Unspecified	Relapse at 11 m
Harril WC et al [2] 1996 USA	F 46 yo DM2	Yes	Yes	None	Surg AmB 650 mg	8 m	Unspecified	Without relapse at 21 m
Waizel-Haiat S et al. [14] 2003 Mexico	F 66 yo DM2	No	No	None	Surg AmB	6 wk	Unspecified	Died of lung cancer
Scharf JL et al [5] 2004 USA	M 57 yo DM2	No	Yes	None	Surg AmB 2.32 g.	3 m	Unspecified	Without relapse at 12 m
Hemashettar BM et. al. [4] 2011 India	M 33 yo Immunocompetent	Unspecified	Unspecified	*Rhizopus* spp.	Surg AmB 1 g/ d (liposomal)	9 m	4 m	Without relapse at 4 m
	M 18 yo immunocompetent	Unspecified	Unspecified	*Mucor irregularis (Rhizomucor variabilis)*	Surg Fluconazole[c]	7 y	67 d	Without relapse at 6 m
Dusart A et al [7] 2013 Belgium	M 64 yo Panhypopituitarism well controlled.	Yes	Yes	None	None[d]	10 m	None	Died
Dimaka K et al [1] 2014 Greece	M 85 yo DM2	Unspecified	Unspecified	None	AmB liposomal[e]/ posaconazole	6 m	3 wk/2wk	Without relapse at 6 m
Angali et al [6] 2014 India	M 18 Immunocompetent	No	No	None	Surg AmB liposomal 2.5 g/Itraconazol	1.5 m	10 d	Died
Gutierrez-Delgado et al 2015 Mexico	M 47 DM2	No	No	None	Surg AmB 2.575 mg	3 m	26 d	Without relapse at 4 m

M:male, F: female, yo: years old, Surg: surgical debridement, AmB: Amphotericin B, DM: diabetes mellitus, DKA: diabetic ketoacidosis.
[a] Patient without surgical treatment because of bad prognosis due to the great extension of the disease.
[b] No amphotericin was administered to the patient.
[c] The authors emphasize the lack of utility of fluconazole in this case; evidenced with the resistance in vitro of this strain to fluconazole, also emphasize effectiveness of the wide surgical debridement.
[d] The diagnosis was made postmortem.
[e] Patient without surgical treatment because of the high cardiovascular risk.

within 10 days of evolution [2].

Species of the genera *Rhizopus* and *Mucor* are more commonly isolated [4]. The causative agent is isolated in only 20% of acute cases and in less than 11% of chronic cases [2]. In our review only 5 of 23 patients (21.7%) the causal agent was isolated. It is possible that in chronic infection, the causative agent may show a decreased ability to grow at body temperature, compromising their angioinvasive nature. [1,5].

Macroscopically it is characterized by tissue necrosis [5,11]. Definitive diagnosis requires the microscopic identification of the fungus in tissue specimens [1]. Histologically, findings are invasive hyphae, non-septated, with 90° angle branching corresponding to the fungi in the order of Mucorales [2]. Hyphae can be identified by hematoxylin-eosin stain technique, but are more clearly seen in PAS o Grocott-Gromori methenamine-silver nitrate [9]. Occasionally, a granuloma formation can be found, as was in this case. [5,11,16].

Differential diagnoses include chronic bacterial sinusitis, sinonasal and orbital neoplasms, granulomatous disease, Grave's disease, pseudotumor or cavernous sinus thrombosis [1].

Treatment is similar in both presentations, including wide surgical debridement of involved tissue and systemic amphotericin B therapy with control of underlying comorbid factors. [1,2,6] Therapy lasts until there is no evidence of progression of the disease [6]. One study reported 8 months therapy with liposomal amphotericin with minor changes in renal function [17].

Relapse is characterized by new-onset of symptoms for $\leq$4 weeks after symptom resolution and recurrence for >5 weeks after resolution. In literature, recurrence has been reported in 33% of the cases [2] and relapse in 13% with a mean of 23 months (range 11–26 mo) after infection resolution. Computed tomography (CT) is recommended a month after finishing treatment and repeat CT every 3–4 months [6]. Some authors suggest magnetic resonance imaging [14], as well as endoscopy every 2–3 months for screening [6]. Nonetheless, we recommend a 36 months follow-up, due to this is the time that the relapses or the surveillance had been reported [11,15].

General survival rate in chronic presentation is reported in 83% of patients, compared to 10–35% in acute. [1,2,4] However, studies show that in patients with dual therapy with surgical debridement and amphotericin B, survival rate escalated to 91%. For this reason, we recommend both surgical and antibiotic therapy for prevention of severe outcomes.

4. Conclusion

Chronic rhinocerebral mucormycosis is a rare presentation that requires a high index of suspicion due to atypical presentations. Mucormycosis is an opportunistic infection that affects mainly immunocompromised patients with a decreased ability to phagocytize, commonly observed in diabetic ketoacidosis, hematological neoplasms, chemotherapy-induced neutropenia, and use of deferoxamine. Therefore in cases of persistent nasal congestion or ocular/facial pain associated with the mentioned risk factors and no clear cause of the symptoms in an otherwise immunocompetent patient, mucormycosis should be considered as causative agent.

Ethical approval

The local ethics committee approved the publications of this case under the number IF-15006.

Funding

We thank the University Hospital “Dr. Jose Eleuterio Gonzalez” of the Autonomous University of Nuevo Leon, Monterrey México for the support on the realization of this article.

Author contribution

Collection, analysis and interpretation of the data, study design, writing of the manuscript: Eva M Gutiérrez-Delgado; Collection, analysis and interpretation of the data, writing of the manuscript: Reynaldo Lara-Medrano, study design, analysis and interpretation of the data: Javier Ramos-Jiménez; surgical treatment of the patient and study design: Adolfo Montemayor-Alatorre; surgical treatment of the patient and study design: Jose Luis Treviño-González; interpretation of pathology results and study design: Luis A Ceceñas-Falcón; interpretation of pathology results and collection of the data: Eduardo Ruiz-Holguín; collection of the data and contributor Andrade-Vázquez Catalina J.

Conflicts of interest

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Consent

The local ethics committee exempted this group of word of the need of consent, due to the privacy of the patient is not involved, besides the publication of this case do not altered the treatment of the patient and the decision of the publication was made after the medical condition of the patient was solved.

Registration of research studies

This is a case report and a review of the literature.

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