Risk Factors Associated with Morbidity and Mortality of Acute Invasive Fungal Rhinosinusitis

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Abstract

Acute invasive fungal rhinosinusitis (RSFIA) is a potentially lethal disease that occurs in immunocompromised patients who have a rapidly progressive evolution to adjacent structures in a disseminated infection and death of the patient. Material and Methods: An observational, cross-sectional, retrospective, analytical study was designed. There were 19 patients diagnosed with Acute Invasive Fungal Rhinosinusitis, we considered the risk factors associated with morbidity and mortality, such as age, gender, comorbidities, immunocompromise. Results: 94.74% had diabetes mellitus and 21.05% had chronic kidney disease. The most frequent agent was Mucormycosis 78.95%, followed by 15.79% for Aspergillus. 89.47% underwent surgical debridement. Mortality was estimated at 42.11%. The following associations with mortality were found: age equal to or greater than 65 years Student's T-score of -2.1 and p0.04, the visual and state of consciousness alteration had a p 0.01, p 0.02 and p 0.008 with RR of 3.61 (95% CI 1.25 - 10.37), RR of 5.09 (95% CI 0.77 - 35.59) and RR of 3.75 (95% CI 1.62 - 8.67)) respectively. Necrosis of the hard palate showed a p-value of 0.04; RR of 2.8 (95% CI 1.09 - 7.14). Bone erosion by CT p 0.03; RR (95% CI 0.88 - 12.51). Conclusions: The variables associated with mortality cases are older than 65 years, altered state of consciousness, diplopia, decreased visual acuity, hard palate necrosis and bone erosion. While the only protective factor to mortality identified was early surgical debridement, decreasing the mortality event up to three times. Keywords: Acute invasive fungal rhinosinusitis; Mucormycosis; Mortality; Associated factors.

Abbreviations: AIFR: Acute Invasive Fungal Rhinosinusitis TC: Computed Tomography, DM: Diabetes mellitus, CKD: Chronic kidney disease, LV: Liver disease, LK Leukemia

INTRODUCTION

Rhinosinusitis comprises a spectrum of inflammatory and infectious diseases that involve one or more of the paranasal sinuses and nasal mucosa, various etiologies are known (infectious, allergic or mechanical obstruction, other less common, hypersensitivity to aspirin and cystic fibrosis). Fungal or fungal rhinosinusitis (RSF) is a clinical entity not so rare as it is believed, it was recognized more than a century ago, but it is only 1 or 2 decades ago that it is fully described and classified.1, Based on

the clinical manifestations, histopathology, radiology and mycological characteristics are classified to the Fungal Rhinosinusitis in these two basic forms of presentation (NEW ENGLAND 1998): Acute Invasive Fungal Rhinosinusitis

Non-invasive form: clinical condition of relatively benign presentation and includes three entities: Allergic fungal rhinosinusitis, Mycetoma or fungal ball and saprophytic colonization Invasive form: has a more aggressive clinical course and may be presented as: Invasive acute, Invasive chronic and Invasive

granulomatous. 1, 2 The main infectious agents of rhinosinusitis are attributed to viruses, bacteria and fungi; multiple fungal organisms have been reported as causative agents of fungal rhinosinusitis, however, the most frequent agents are saprophytic fungi (Mucorales) among the most commonly identified species are Mucor spp, Rhizopus sp, Lichteimia (Absidia) and Corymbifera. 1, 2, Rhinosinusitis (RSFIA) or Fulminant (Mucormycosis),

refers to fungal infections caused by members of the order Mucorales, the infection is given by inhalation through aspiration of spores or by direct inoculation into the skin or mucous They are vasotropic microorganisms, so they have the ability to cause tissue infarcts. 3 RSFIA is a potentially lethal disease which mainly occurs in immunocompromised patients (around 2%), although it can also occur in immunocompetent patients in whom development is chronic and indolent, unlike immunocompromised patients in whom it has an evolution rapidly progressing to adjacent structures such as the orbit, cavernous sinus and brain, culminating in a disseminated infection and death of the patient. 5, 6 Some predisposing factors for the development of this disease are diabetes, diabetic ketoacidosis, sepsis, renal failure, intravenous drug use, neutropenia, deferoxamine therapy, burns, trauma, chemotherapy, therapies with high concentrations of steroids, cirrhosis, lymphomas, leukemia, hepatitis and myelodysplastic syndromes. 7 Some examples in which the presentation of the disease is favored is the case of diabetic patients, since monocytes and macrophages fail in the function of suppressing germination of the spores. Diabetic ketoacidosis alters the functions of neutrophils, including chemotaxis, adhesion and their oxidative function. The metabolism of iron is also a critical factor in the pathogenesis of patients with diabetes at risk of suffering from mucormycosis. 8 The performance of a histopathological study is necessary for the diagnosis, in which the mucosa is biopsied during an endoscopy, in which findings such as pale mucosa, ulcers and granulation can be found in up to 75% of the cases, in addition to data of ischemia and necrosis in severe cases. 9 The biopsy of the middle turbinate has been proposed before the disease is fully established as an early diagnostic method, since it has been identified that the invasion of this intranasal structure is more commonly invaded. 9 After inhaling the spores and depositing them in the sinuses, the infection can spread

to the orbit and brain tissue. The initial symptoms of the disease are usually not very specific such as fever, nasal obstruction and rhinorrhea; some more serious symptoms can include visual affection, paresthesias and other cranial neuropathies (mainly V and VII), these represent manifestations later in patients with more advanced disease. 9, 10 The rhino-orbitocerebral presentation, represents the form of greater invasion of the disease, has three stages of progression: limited to the sinonasal region, extended to the rhino-orbital region and includes the rhino-orbitocerebral component. As the infection travels through the vascular tissues and adjacent soft tissues, the vessels become thrombosed and vascular occlusion occurs, which causes infarction and necrotizing vasculitis of the structures. This localized ischemia environment produces the acidic environment necessary for fungal growth. 7 RSFIA is a rapidly progressive disease that predisposes to high rates of morbidity and mortality. Despite treatments, 50 to 80% mortality has been reported in patients treated for RSFIA; the progression of initial symptoms to those that make the disease evident can be so aggressive that the transition occurs up to one day. 8, 9, 10

Unlike orbital apex syndrome, in the orbital fissure syndrome, vision is preserved, given that the optic foramen is intact.3 If the infection continues ascending, the fungus can reach the cavernous sinus and by contiguity the brain parenchyma provoking thrombosis and infarcts that subsequently evolved to coma and death of the patient. 9, 10 The presentation of exclusively nasal RSFIA has lower mortality rates, unlike those patients in whom intracranial structures are involved, these rates are doubled11. Some of the differential diagnoses to be taken into account when presenting nasal symptoms are the granuloma of the line media, rhinoscleroma, syphilis, tuberculosis, sinonasal and orbital tumors. 10 In the case of ocular and cephalic involvement, it should be differentiated from temporal arteritis, orbital cellulitis, cavernous sinus thrombosis and Pseudomonas sinusitis. 10 The management of this disease is multidisciplinary, since it deals with the correction of the underlying disease, early antifungal treatment, as well as aggressive surgical debridement for its resolution. 9.10 Debridement by laparoscopy with biopsy is a therapeutic diagnostic method which allows identifying the quality of the mucosa, taking samples and debriding the affected area. Standard stains for

mucorales are hematoxylin-eosin, periodic acid-Schiff and Gomori silver metamine. 10, 11 The advantage of an aggressive debridement is to remove the devitalized tissue caused by the angiocentric necrosis caused by the fungus, in addition to providing the affected surface with a better area for the scope of the medical treatment, since the occlusion is released. blood vessels and has a better pharmacological distribution. 9, 10, 11 If the affectation is very serious, daily debridements can be used; if the extension covers the orbit, ocular exenteration or even sinus removal may be necessary. 9, 10, 11 The preferred imaging technique to establish soft tissue invasion is magnetic resonance, since it allows a more accurate determination of the area affected by the infection, the use of the tomography delimits the invaded bone portions, with The disadvantage of having limited sensitivity in the identification of early stages of infection is also used to observe the laterality (unilateral, bilateral) of the disease and the expansion of the affected paranasal sinuses. 9, 10 The histopathological characteristics that are observed is the presence of the rupture of the mucosa by the agent and tissue necrosis, there may be invasion of the blood vessels causing angiocentric necrosis. 9, 10, 11 There have been several clinical trials in which it has been seen that the best antifungal therapy for these cases is with the use of amphotericin B lipid formulation, however, in cases of patients with kidney involvement can bring controversy its use, for which the use of Posaconazole as a second therapeutic option has been described.10, 11

The presence of symptoms varies according to the affected sinuses; the presence of invasion in the ethmoid sinus tends to a rapid dissemination to the brain tissue through the papyracea lamina, the infection of the maxillary sinus will be reflected with the presence of palatal involvement, the frontal sinus is the one that has been reported with less affectation. 9.10

If the infection crosses the ethmoid sinus into the papyracea lamina and subsequently reaches the orbit and its contents, it can easily spread to the posterior region and cause the orbital apex syndrome. 9 The orbital apex syndrome is an atypical presentation involving the involvement of the cranial nerves II, III, IV and VI, as well as the ophthalmic branch of the V-pair and is characterized by the sudden loss of vision, ophthalmoplegia, palpebral ptosis, optic atrophy, hyperesthesia or hypesthesia in the distribution of V1, swelling and proptosis of the eyelid, optic dilation and diplopia

There are proposals to make the diagnosis by less invasive methods, in a study conducted in 2014 the usefulness of the Polymerase Chain Reaction (PCR) and some immunological methods directed towards specific agents was determined, however, the observation by direct microscopy of The affected tissues continues to be the best technique for the diagnosis of these patients. 12 The determination of the prognosis occurs to a large extent with the promptness of the diagnosis, since there are no clear data indicating a clearer predisposition among immunocompromised patients, in addition to the poorly determining presentation of the symptoms; special measures have been taken in which it is proposed to suspect RSFIA in all patients with compatible symptoms and to begin the search for the diagnosis to improve the prognosis and decrease the morbidity and mortality of those in whom the disease is confirmed in order to initiate an opportune treatment through the techniques already mentioned, but especially the correction in the state of immunosuppression. 15, 16, 17, 18 The mortality rate depends on the underlying disease and the moment of diagnosis, which determines early medical and surgical intervention, which limits the progression and unfavorable outcome for the patient. 14, 15, 16, 17.19

MATERIALS AND METHODS

Study Design

An observational, cross-sectional, retrospective, analytical study was designed in the Specialty Hospital No 2, "Lic. Luis Donaldo Colosio Murrieta" Mexican Institute of Social Security, Sonora, Mexico in a period from January 01, 2011 to July 31, 2017. Cases of patients diagnosed with acute invasive fungal rhinosinusitis who had a complete file were taken into account, sociodemographic and determinant data were included for the development and progression of the disease.

Measurement and Variables

The statistical analysis obtained an Odds Ratio as a measure of association with 95% CI, between comorbidities vs other associated variables, an X2 for qualitative variables and a Student's T for quantitative variables with p <0.05 for statistical significance. Univariate analysis was performed applying the measures of central tendency (mean and median), and dispersion measures (standard deviation), as appropriate for parametric and non-parametric variables, as well as proportions for qualitative variables.

A bivariate analysis was performed for qualitative variables, as well as an association of risk between the variables, obtaining an Odds Ratio between the immunosuppressive cause against the variables, determining the groups with the highest risk of morbidity and mortality.

Statistical Methods

Additionally, an X2 was performed for qualitative variables, and a Student's T for quantitative variables with p <0.05 for statistical significance. Everything was exported to the statistical program Epi-Info 7, which is a program of free use that does not require a license for its management.

Ethical Procedures

The procedures were performed according to the Declaration of Helsinki and approved by the Ethics Committee of Specialty Hospital No 2, "Lic. Luis Donaldo Colosio Murrieta" Mexican Institute of Social Security

Setting

The study was conducted at the Department of Otorhinolaryngology and Head and Neck Surgery in Specialty Hospital No 2, "Lic. Luis Donaldo Colosio Murrieta" Mexican Institute of Social Security

RESULTS

In our study, a total of 19 patients were included, where the average age recorded was 57 years, a minimum of 35 years and a maximum of 82 years. The distribution by sex was 52.64% female and 47.37% male (graphic1). Within the registered comorbidities,

94.74% of the patients presented diabetes mellitus, another 21.05% Chronic Renal Disease (Table 1)

In the distribution by year, during 2017 a total of 10 cases were registered, in 2013, 2014 and 2016, 3 cases for each year (graph 2).

The distribution by state, we found that 52.63% correspond to the state of Sinaloa, secondly, 36.84% for the state of Sonora, and in Baja California Sur 10.53% were registered

Through the pathology results, the fungal strain was identified, 78.95% corresponded to the agent Mucormycosis, followed by 15.79% for Aspergillus, and in third place with 5.26% Candida + Mucormycosis (Table 2).

The clinical distribution of the disease was classified by the clinical and tomographic findings, as well as the surgical findings, firstly in the Sinonasal area, with 36.84%, secondly the Rinoorbital area with 31.58%, and in third place

Rinoorbitocerebral with 26.32% of the cases (graph 3)

The changes in blood count at the leukocyte level were evaluated, essentially neutrophils, where an average of 16.76 was recorded, with a minimum of 2 and a maximum of 42.2. The time in having the definitive diagnosis was evaluated, where the mean was 3.15 days, with a minimum of 1 day, and a maximum of 9 days The therapy start time was also measured in days, in which an average of 2.73 days was registered, with an average of 1 day, and a maximum of 7 days

In 89.47% of patients underwent endoscopic surgical debridement, and 10.53% did not. Patients who underwent ocular exenteration were 31.58% and 68.42% did not. cases of mortality are estimated at 42.11% In the case of resolution of the table, it was observed that 36.84% was total and 21.05% with sequelae

With a univariate statistical analysis, the association and dependence between variables was determined. The association with the type of strain isolated with mortality, we obtained a value of X2 of 1.49, with a p 0.47, not significant

The clinical form with mortality was observed a greater mortality in the Rinoorbitocerebral type, with a p 0.08, without statistical significance, gender with mortality, a p of 0.84, without statistical significance, the calculation of relative risk (RR) , a value of 0.9 was obtained (IC 95% 0.31 - 2.58) IC95% considered as indeterminate

The mortality association with ocular exenteration was p = 0.59, without finding statistical significance, the RR value was 0.72 (95% CI 0.2 - 2.58), 95% CI was undetermined

Surgical debridement with mortality yielded a p <0.07 not significant; the RR estimate was 0.35 (95% CI 0.18 - 0.67) 95% CI, considering it a protective factor towards mortality. Age and mortality were observed in a mean of 65 years or more, with a Student's T value of -2.1 and p 0.04, which was statistically significant. In the total neutrophil count, a very high mean was obtained. similar in both cases, the difference was 1.45, with a T value of -0.3 and a p 0.76, being not significant

The initiation of antifungal therapy had, with a T value of 0.68 and a p 0.5, without significance

The distribution of symptoms presented by the most common patients are headache and facial pain, occurring in 68.42% of patients, secondly, nasal congestion and decreased visual acuity are observed, these symptoms affect 57% , and thirdly, Ophthalmoplegia was identified with a proportion of 52.63%. In the cases of the signs presented by the patients, it was determined that the first place is necrosis of the middle turbinate, since 78.95% presented, secondly, the necrosis of the nasal septum, represented by 42.11%, while in third place the necrosis of the inferior turbinate was identified, with 36.84% The distribution of the findings by tomography were also identified, where 89.47% had occupation of the maxillary sinus, followed by occupation of the ethmoidal sinus with 84.21%, and thirdly, bone erosion and orbital extension were observed with 47.37%.

The diplopia, decrease in visual acuity and alteration of the state of consciousness have presented dependence with the mortality of patients, with a value of $p = 0.01$, $p = 0.02$ and $p = 0.008$ respectively, are considered as statistically significant, At the same time, the estimation of relative risk confirms the association of risk, where, the values obtained can be confirmed with a RR of 3.61 (95% CI 1.25 - 10.37) for diplopia, while for the decreased visual acuity, a RR of 5.09 (95% CI 0.77 - 35.59) and RR of 3.75 (95% CI 1.62 - 8.67) was obtained for the alteration of the state of consciousness (table 4)

The only clinical sign with significance was necrosis of the hard palate, with a p-value of 0.04; an estimated RR value of 2.8 (95% CI 1.09 - 7.14), 95% CI is considered a risk factor for mortality (Table 5) Finally, the association of tomographic findings in association with mortality , determined that only the presence of bone erosion was statistically significant, p 0.03
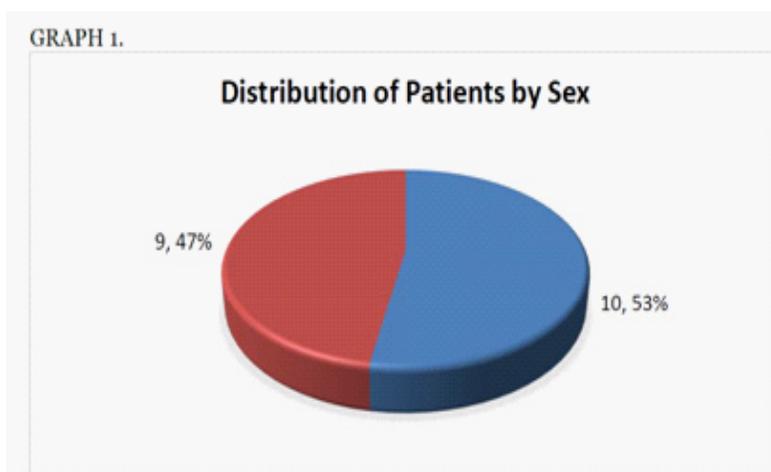
GRAPH 1.

Distribution of Patients by Sex

9, 47%

10, 53%

Source: Department of Otolaryngology of the UMAE IMSS, Sonora, México.

TABLE1.

Comorbidities	Frequency	Percent	Cum. Percent	Exact 95% LCL	Exact 95% LCL
DM2	18	94,74%	100,00%	73,97%	99,87%
ERC	4	21,05%	21,05%	6,05%	45,57%
Liver Disease	1	5,26%	26,32%	0,13%	26,03%
Leukemia	1	5,26%	31,58%	0,13%	26,03%
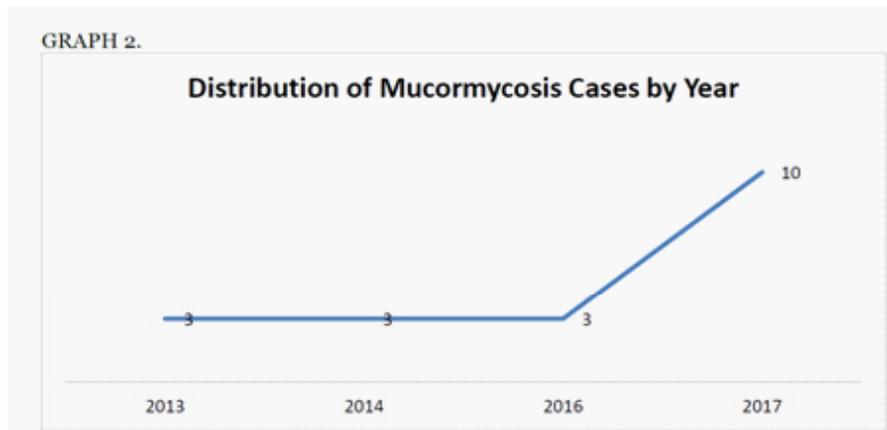
Distribution of Comorbidities

Source: Department of Otolaryngology of the UMAE IMSS, Sonora, México.

GRAPH 2.

Distribution of Mucormycosis Cases by Year

Source: Department of Otolaryngology of the UMAE IMSS, Sonora, México.

GRAPH 3.

Clinical distribution of the disease

- RHINOCEREBRA
- RHINORBITAL
- RHINOORBITOCEREBRAL
- SINONASAL
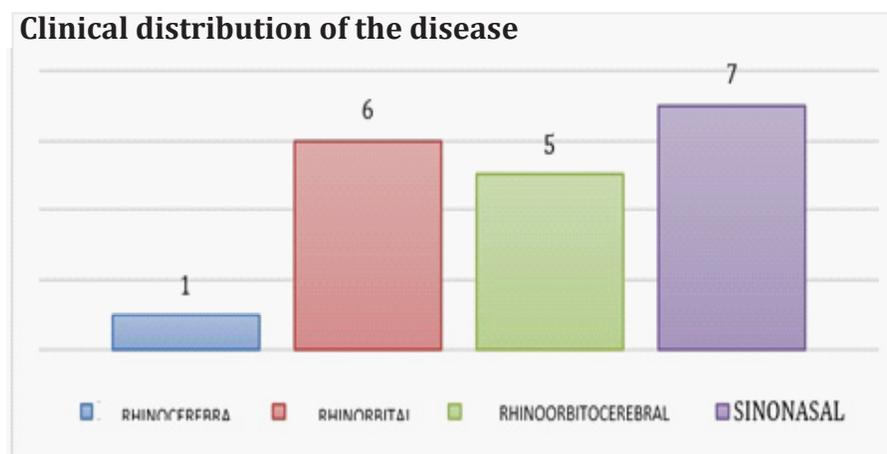
Source: Department of Otolaryngology of the UMAE IMSS, Sonora, México.

TABLE 4.

Distribution of Symptoms in Association to Mortality

Symptom	Mortality	X2	p	RR	IC 95% Min	IC95% Max
Alteration of the State of Consciousness	4	6,96	0,008	3,75	1,62	8,67
Headache	6	0,27	0,59	1,38	0,38	4,95
Periorbital cellulitis	5	1,26	0,25	1,85	0,6	5,63
Nasal congestion	5	0,12	0,72	1,21	0,4	3,65
Diplopia	5	6,11	0,01	3,61	1,25	10,37
Decrease Visual Acuity	7	4,96	0,02	5,09	0,77	35,59
Facial pain	7	2,32	0,12	3,25	0,5	20,72
Facial edema	2	0,88	0,34	1,77	0,64	4,93
Epistaxis	0	0	1	SN	SN	SN
Fever	3	0,22	0,63	1,3	0,45	3,78
Facial Hypoesthesia	3	0,89	0,34	1,68	0,61	4,58
Ophthalmoplegia	6	2,77	0,09	2,7	0,71	10,13
Facial paralysis	0	NS	NS	NS	NS	NS
Purulent Rinorrea	4	1,02	0,31	1,71	0,61	4,78
Orbital Apex Syndrome	4	1,02	0,31	1,71	0,61	4,78

Source: Department of Otolaryngology of the UMAE IMSS, Sonora, México.

TABLE 5.

Symptom	Mortality	X2	p	RR	IC 95% Min	IC95% Max
Distribution of Signs in Association to Mortality						
Lower Corneal Necrosis	4	1,02	0,31	1,71	0,61	4,78
Middle Corneal Necrosis	6	0,12	0,71	0,8	0,25	2,55
Hard Palate Necrosis	4	3,99	0,04	2,8	1,09	7,14
Nasal Septum Necrosis	4	0,35	0,55	1,37	0,48	3,9
Lower Corneal Paleness	1	0,6	0,43	0,53	0,09	3,18
Pale Medium Corneal	0	NS	NS	NS	NS	NS
Palate Hard Palate	1	1,45	0,22	2,57	1,44	4,58
Pale Septum Nasal	3	0,89	0,34	1,68	0,61	4,58
Lower Cornete Ulcer	0	NS	NS	NS	NS	NS
Half Cornete Ulcer	0	NS	NS	NS	NS	NS
Hard Palate Ulcer	2	0,88	0,34	1,77	0,64	4,93
Ulcer Nasal Septum	1	0,05	0,81	1,21	0,27	5,43

Source: Department of Otolaryngology of the UMAE IMSS, Sonora, México.

DISCUSSION

Acute invasive fungal rhinosinusitis is a documented disease that occurs in 2% of patients with immunocompromise; in this study, it was determined that 5.26% of patients had a disease that generated an immunocompromise (particularly Leukemia), this proportion is much lower than that reported by other authors such as Sakeena J. Payne and Süheyla KÖMÜR with 52.9-91%, possibly related to our short series of cases 2, 15.

The most common comorbidities that came to present our series of cases, was Diabetes Mellitus type 2, with 94% of patients, similar to that reported by Ebru Kursun and Hyo-Lim Hong, being the most common condition diabetes mellitus (67- 71%), chronic kidney disease (7%), immunosuppression or transplants (4%) 3, 14.

It is also important to note that the average age of the patients was 57 years, which gives them an age group that has the condition to develop this type of comorbidities 14.

The main infectious agents are attributed to viruses, bacteria and fungi; cases have been reported of several causative agents, however, in fungal rhinosinusitis the most commonly identified correspond to the Aspergillus and Mukor group, based on what Midhat Amin and Sakeena L. Payne 1, 2 have mentioned. These authors mention that Mucormycosis are infections caused by members of the Mucorales order. Similar to what was found in our cases where Mucormycosis was identified as the main causative agent 78.95%, followed by Aspergillus in 15.79%, only 5.26 of the patients presented a combination between Candida and Mucormycosis. 8

At present, the mortality rate has been significantly reduced from 80-90% to 20-40% in diabetic patients7; authors such as Sakeena J. Payne and Maria N. Gameletsou, have managed to determine that this mortality rate oscillates between 80% despite radical and aggressive therapies, rhinocerebral mucormycosis continues to be associated with a fulminant course of the disease and with a mortality very high.

On the other hand, Maria N. Gamaletsou, Nikolaos V. Sipsas, mention that the RSFA is a rapidly progressive disease that predisposes to high rates of morbidity and mortality despite the treatments, they have described a 50 to 80% mortality in RSFA treated patients; the progression of initial symptoms to those who make the disease evident can be so aggressive that the transition occurs up to one day 2, 8. In our series of cases, the average time of care, from diagnosis to the start of treatment, presented an average of 2.73 days. Derived from the above, our Registered Mortality for this disease was 42.11%, which is below that reported by other hospitals, the international medical literature, mentions that the progression of the disease is rapid,

with various symptoms ; the mean time of diagnosis of the patients in our hospital was 3.15 days, with a beginning of medical treatment at 2.73 days since the diagnosis, it can be considered that the time between diagnosis and treatment is relatively short , this finding may be decisive in reducing the Mortality rate. It was also possible to identify that 21.05% of the patients presented healing of the picture, but with the presence of sequelae, while 36.84% of them presented a total cure.

It has been documented in the article published by Michael A. DiBartolo and Patrick S. Kelley, where it is established that as the infection travels through the vascular tissues and adjacent soft

tissue, the vessels become thrombi and it is produced vascular occlusion, which generates infarction and necrotizing vasculitis of nearby structures 7, which conditions the main symptoms in patients who are headache, facial pain, nasal congestion, decreased visual acuity; the most common clinical signs are necrosis of the middle turbinate and necrosis of the nasal and inferior septum, while the findings recorded by CT involved the maxillary and ethmoidal sinuses.

Based on what Cortney Y. Kauh, Christine C. Nelson and Raquel Artal, Beatriz Ágreda mention in their article, it is established that when the extension of the infection continues towards the posterior anatomical areas, the Fungus can access the cavernous sinus and by contiguity to the cerebral parenchyma, thrombosis and infarcts that subsequently evolved to coma and death of the patient 9, 10.

By means of the statistical association, it has been determined that the alteration of the state of consciousness suggests a true risk of mortality, even tripling the event, as well as diplopia, where the event associated with mortality also triples, which makes us think of a greater concern for patients who come to present these two symptoms; it could be considered that the decrease in visual acuity also presents a similar situation, but it is not very clear.

Patients with a hard palate necrosis also have to have a much closer follow-up, since these have also been identified with a higher risk of mortality, where the event also occurs up to 2.8 times. The tomographic findings the only relevant one that was associated was the bone erosion, but it has also not been possible to determine the magnitude, only the dependence of it.

One of the sociodemographic characteristics that has obtained a statistical significance is age, associating a higher mortality in patients with an average age of 65 years, while those who survive have a mean age of 51 years, this suggests that younger patients have greater chance of survival and cure. The distribution by sex has not been determinant in the final results of the patients, which prevails that the patients have the same possibility of mortality, cure, and / or sequelae, whether men or women.

It is also remarkable to comment on what Ignacio J. Fernandez and Fabiana C.P. Valera on surgical debridement, which is a therapeutic diagnostic technique that allows identifying the quality of the mucosa, taking samples and removing the affected area 4,5. In our work, what has been determined, is the fact that serial and timely surgical debridement is a protective factor to mortality.

The purpose of this research study was to determine the risk factors associated with morbidity and mortality, however, the very nature of the study in association with its low incidence could generate some type of information bias. It could be considered that the timely detection of this type of patients in subsequent years, integrated into this project, could increase the sample size, generating an increase in accuracy and decreasing the information bias, therefore, it is considered that The present work is only the beginning in the search for risk factors associated with morbi-mortality of invasive fungal *Copyrights* @ rhinosinusitis ***Ljiljana Š, et.al.*** in northwestern Mexico.

We will quote one of the criteria of Bradford Hill causality, which establishes the strength of association: The strength of association is measured by the magnitude of the ratio between rates, means and / or incidents. If the rate, average and / or incidence of an event among those exposed to a cause is much higher than the rate, average and / or incidence among those not exposed, it is established that there is a greater strength of association, this association has been evaluated and determined by two statistical tests in this project, therefore its veracity and reliability are accepted.

Limitations of the Study

The limitations of this study is its small sample of patients, these results can be useful to continue recruiting a larger number of patients and obtain a more representative sample, giving results with greater validity

Conclusion

The average age of patients with this condition is 57 years, the distribution by gender is homogeneous. The most common comorbidity is diabetes mellitus. The main entities found in the northwest region were Sinaloa, Sonora and Baja California Sur respectively.

The most frequent causative agent is Mucormycosis; while the most common clinical form were sinonasal and rhinoorbital. The mean time of diagnosis was 3 days, with a start of treatment at 2.7 days.

The incidence of mortality was 8 patients from 19 patients in the period from 2013 to 2017, which represents 42% of the total, 21% of the patients presented healing with sequelae, and 36.84% presented total healing.

The associated variables that present dependence and association to mortality cases are older than 65 years, altered state of consciousness, diplopia, decreased visual acuity, hard palate necrosis and bone erosion. While the only protective factor to mortality identified was surgical debridement, decreasing the mortality event up to three times.

Our presented results show very interesting data, however we must deduce that this is a study with a series of cases, which requires a larger number of patients to obtain conclusions with greater veracity, it is proposed to increase the number of cases to this series in our hospital, recruiting patients diagnosed with this condition over the next few years

References

[1] Amin M, Kakru DK, Wani T, Qazi SM. Fungal Rhinosinusitis: Period prevalence and risk factors – A prospective study. JK Pract 2012; 17 (1-3): 33-38. Disponible en http://medind.nic.in/jab/t12/i1/jabt12i1p33.pdf

[2] Payne SJ, Mitzner R, Sudhir Kunchala, Roland L, McGinn JD. Acute Invasive Fungal Rhinosinusitis: A 15-Year Experience with 41 Patients. Otolaryngol Head Neck Surg 2016 Jul 22;154 (4): 759–764. Disponible en http://journals.sagepub.com/doi/pdf/10.1177/0194599815627786

[3] Kursun E, Turunc T, Demiroglu YZ, Arslan AH. Evaluation of 28 cases of mucormycosis. Mycoses 2015; 58 (2): 82-7. Disponible en https://www.escmid.org/escmid_publications/escmid_elibrary/mater ial/?mid=1623

[4] Fernandez IJ, Stanzani M, Tolomelli G, Paaquini E, Vianelli N, Baccarani M, et al. Sinonasal risk factors for the development of invasive fungal sinusitis in hematological patients: Are they important. Allergy Rhinol 2011; 2 (1): 6–11. Disponible en https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3390131/

[5] Valera FC, do Lago T, Tamashiro E, Yassuda CC, Silveira F, AnselmoLima WT. Prognosis of acute invasive fungal rhinosinusitis related to underlying disease. Int J Infect Dis 2011; 15 (1): 841–844. Disponible en https://www.ncbi.nlm.nih.gov/pubmed/21963345

[6] Ogawa T, Takezawa K, Tojima I, Shibayama M, Kouzaki H, Ishida M, et al. Successful treatment of rhino-orbital mucormycosis by a new combination therapy with liposomal amphotericin B and micafungin. Auris Nasus Larynx 2012; 39 (2): 224-8. Disponible en https://www.ncbi.nlm.nih.gov/pubmed/21592699

[7] DiBartolo MA, Kelley PS. Rhino-Orbital-Cerebral Mucormycosis (ROCM): A Comprehensive Case Review. Aviat Space Environ Med 2011; 82 (1): 913–6. Disponible en https://www.ncbi.nlm.nih.gov/pubmed/21888278

[8] Gamaletsou MN, Sipsas NV, Roilides E, Walsh TJ. Rhino-OrbitalCerebral Mucormycosis. Curr Infect Dis Rep 2012 Jun 10; 14 (1): 423–434. Disponible en https://www.ncbi.nlm.nih.gov/pubmed/22684277

[9] Kauh CY, Nelson CC, Fekrat S, Scott IU. Diagnosis and management of orbital mucormycosis. Eyenet Magazine 2014; 1 (1): 37-39. Disponible en https://www.aao.org/eyenet/article/diagnosis-management-of-orbital-mucormycosis

[10] Artal R, Ágreda B, Serrano E, Alfonso JI, Vallés H. Rhinocerebral mucormycosis: Report on eight cases. Acta Otorrinolaringol Esp 2010; 61 (4): 301–305. Disponible en http://www.sciencedirect.com/science/article/pii/S217357351070053 3

[11] Frost CJ, De Jesus RO, Massini TC, Schmalfuss IM, Mancuso AA. Acute Invasive Fungal Rhinosinusitis: A Comprehensive Update of CT Findings and Design of an Effective Diagnostic Imaging Model. AJNR Am J Neuroradiol 2015; 36 (8): 1529-Disponible en http://www.ajnr.org/content/36/8/1529.long

[12] Badiee P, Moghadami M, Rozbehani H. Comparing immunological and molecular tests with conventional methods in diagnosis of acute invasive fungal rhinosinusitis. J Infect Dev Ctries 2016; 10(1): 090-095. Disponible en https://jidc.org/index.php/journal/article/view/26829542/1444 *Copyrights@ **Portillo Flores, et.al.***

[13] Cofré F, Villarroel M, Castellón L, Santolaya ME. Tratamiento exitoso de una mucormicosis rinocerebral persistente en un paciente pediátrico durante el debut de una leucemia aguda. Rev Chilena Infectol 2015; 32 (4): 458-463. Disponible en http://www.scielo.cl/pdf/rci/v32n4/art15.pdf

[14] Hong HL, Lee YM, Kim T, Lee JY, Chung YS, Kim MN, et al. Risk Factors for Mortality in Patients with Invasive Mucormycosis. Infect Chemother 2013; 45 (3): 292-298. Disponible en https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3848522/pdf/ic-45292.pdf

[15] Kömür S, İnal AS, Kurtaran B, Ulu A, Uğuz A, Aksu HS, et al. Mucormycosis: a 10-year experience at a tertiary care center in Turkey. Turk J Med Sci 2016; 46: 58-62. Disponible en https://www.researchgate.net/publication/289366406_Mucormycosis_a_10-year_experience_at_a_tertiary_care_center_in_Turkey

[16] Tiraboschi I, Bravo M, Fernandez N, Stecher D, Melero M, Lasala M, et al. Mucormicosis, una micosis emergente. MEDICINA (Buenos Aires) 2012; 72: 23-27. Disponible en http://www.scielo.org.ar/pdf/medba/v72n1/v72n1a06.pdf

[17] Méndez-Tovar LJ, Mejía-Mercado JA, Manzano-Gayosso P, Hernández-Hernández F, López-Martínez R, González IS, et al. Frecuencia de micosis invasivas en un hospital mexicano de alta especialidad. Experiencia de 21 años. Rev Med Inst Mex Seguro Soc 2016; 54 (5): 581-7. Disponible en http://www.medigraphic.com/pdfs/imss/im-2016/im165f.pdf

[18] Vallejo JC, Arellano L, Silva M. Rinosinusitis fúngica: Relato de un caso y revisión de la literatura. Rev Ac Ec ORL 2005; 4 (1): 55-61. Disponible en http://www.aeo.org.ec/Revistas/VOL4%20NO1/8%20sinusitis%20fung ica.pdf