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Invasive rhinosinusal mucormycosis after hematopoietic stem cell transplantation in a myelodysplastic syndrome patient.

Gastélum-Cano JM[1,2], Motolinia-Muñoz Y[1,2], Marín-Corte JC[1,2], Ortega-Amaya ER[1,2], Gordillo-Martínez AM[1,2], Ruiz-Argüelles GJ[1,2,3]

Abstract

Mucormycosis is a pathologic entity, caused for molds belonging to mucorales order; among risk factors are hematological malignancies, hematopoietic stem cell transplantation (HSCT) and treatment with corticosteroids. This article reports the case of a 56-year-old male patient, Mexican mestizo, with type 2 diabetes mellitus (T2DM) and class 2 obesity (BMI 37.38). As a result of pancytopenia, the bone marrow studies disclosed myeloid hyperplasia and features of myelodysplasia. An outpatient allogeneic hematopoietic stem cell transplantation (Allo-HSCT) was performed on January 14th, 2015. After engrafting successfully, on day + 250 pancytopenia due to graft loss ensued. Then, a second outpatient allo-HSCT was made, achieving 100% chimerism. During the aplastic phase, patient developed a rhinosinusal lesion in which the causal agent was identified as *Mucor* sp. It is important to consider HSCT secondary mucormycosis as a risk factor in hematological malignancies patients.

KEYWORDS: mucormycosis; myelodisplastic syndrome; immunosuppression; hematopoyetic stem cell transplantation

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Mucormicosis rinosinusal invasiva después de un trasplante de células hematopoyéticas alogénicas por un síndrome mielodisplásico

Gastélum-Cano JM[1,2], Motolinia-Muñoz Y[1,2], Marín-Corte JC[1,2], Ortega-Amaya ER[1,2], Gordillo-Martínez AM[1,2], Ruiz-Argüelles GJ[1,2,3]

Resumen

La mucormicosis es una enfermedad ocasionada por mohos integrantes del orden de los mucorales; entre los factores de riesgo de padecerla destacan las neoplasias malignas hematológicas, trasplante de células progenitoras hematopoyéticas y tratamiento con corticoesteroides.

[1] Laboratorios Clínicos de Puebla, Puebla, México.
[2] Universidad Popular Autónoma del Estado de Puebla, Puebla, México.
[3] Centro de Hematología y Medicina Interna, Puebla, México.

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Correspondence
Dr. Guillermo Ruiz Argüelles
gruiz1@hsctmexico.com

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Este artículo describe el caso de un paciente de 56 años de edad con diabetes mellitus de un año de evolución y obesidad clase II (IMC 37.38). Con motivo de estudio de pancitopenia se encontró médula hipercelular con hiperplasia de serie mieloide y cambios compatibles con mielodisplasia. Se le realizó trasplante de células hematopoyéticas alogénicas el 14 de enero de 2015. El día +250 sufrió pancitopenia secundaria a pérdida de injerto. Se efectuó un segundo trasplante que logró quimerismo del 100%. Durante la fase aplásica, padeció lesión rinosinusal en la que se identificó como agente causal *Mucor* sp. Es importante considerar las mucormicosis secundarias a trasplante como factor de riesgo en los pacientes con neoplasias hematológicas.

PALABRAS CLAVE: mucormicosis, síndrome mielodisplásico, inmunosupresión, trasplante de células madre hematopoyéticas.

[1] Laboratorios Clínicos de Puebla, Puebla, México.
[2] Universidad Popular Autónoma del Estado de Puebla, Puebla, México.
[3] Centro de Hematología y Medicina Interna, Puebla, México.

Correspondencia
Dr. Guillermo Ruiz Argüelles
gruiz1@hsctmexico.com

INTRODUCTION

Mucormycosis is a pathologic entity, caused by molds belonging to mucorales order with irregularly branched, dichotomous, ribbonlike, aseptate or pauciseptate hyphae, that reproduce sexual by producing zygospores; causing infections with sub-acute, acute and often rapidly progressing invasion.[1,2] The *Mucoraceae* family (comprising *Absidia*, *Mucor*, *Rhizomucor* and *Rhizopus* Genus), is the most common associated with the disease.[3]

Mucorales use to behave as opportunist pathogens. However, they can infect immunocompetent patients. For that purpose, spores must get over histiocytes and neutrophils phagocytosis, which is the most important function for their elimination before developing its invasive form.[4]

Among risk factors for presenting this disease highlights uncontrolled diabetes specially with ketoacidosis manifestation, hematological malignancies, hematopoietic stem cell transplantation (HSCT), treatment with corticosteroids, deep trauma, burnings and chelation therapy with deferoxamine in hemodialysis or transfusion-dependent patients.[1,2]

In recent years, it has been observed an increasing incidence of mucormycosis, because of a growing of vulnerable population like cancer patients and solid organs or hematopoietic transplanted patients.[1,4,5] This represents a serious health problem for patients in HSCT therapy for many diseases, due to the high mortality rates reported for this disease (59-80%).[6-10] Additionally, identification of this etiological agent can be a challenge, owing to that the unique determinant criteria for mucormycosis diagnosis is direct observation of hypha in affected tissue and this could require invasive procedures (bronchoalveolar lavage or biopsy).[5]

Myelodysplastic syndromes (MDS) are a group of indolent clonal ailments which supposes abnormal hematopoietic totipotential cells, and co-exists hypercellular bone marrow with increased hematopoietic cells apoptosis, derived from cytokines excessive production[11] and that frequently results in cytopenia. Infections are common complicacies in MDS and contribute

significantly in mortality of this patients. It is believed that morphological abnormalities in neutrophils are accompanied by functional defects that increase susceptibility for bacterial and fungal infections.[12,13]

The present case describes a male patient, 56 years old, Mexican mestizo, with risk factor of T2DM, severe obesity, immunosuppressive treatment repeatedly and MDS diagnosis, who developed rhinosinusal mucormycosis after two Allo-HSCT.

CASE REPORT

Male patient, 56 years old, Mexican mestizo with obesity class II (BMI 37.38), T2DM with one year of evolution, high blood pressure and hyperuricemia with 3 years of evolution. On December 2014, as a result of pancytopenia, bone marrow biopsy and aspiration was performed in which results showed: CD3 (+) in lymphocytes; CD20 (+) in scarce B-cells; CD34 (+) in endothelial cells; MPO (+) in myeloid cells and Ki67 (+) in 80% of total cells, with diagnosis of myeloid-megakaryocytic hyperplasia and compatible characteristics with myelodysplasia. An outpatient Allo-HSCT was done using cells obtained from a HLA-identical brother in January 14th of 2015; reaching an 85% chimerism on day (D) + 14 after transplant, posteriorly progressing to 100% **(Figure 1)**. On D + 80 patient presented graft versus host disease (GVHD) symptoms grade I that responded to steroids treatment. Later, on D + 250 suffers evidently pancytopenia secondary to graft loss with down of chimerism to 19%. In October 10th of 2015, new bone marrow biopsy and aspiration was indicated. Histopathological results revealed: CD3 (+), CD34 (-), CD15 (+) y MPO (+) in myeloid lineage; CD20 (-) y CD117 (weak; 3.5%) findings of hypercellular BM with hyperplasia in myeloid lineage, compatible outcomes with use of granulocyte colony stimulating factor (G-CSF) additional to reticulin fibrosis grade II. A new

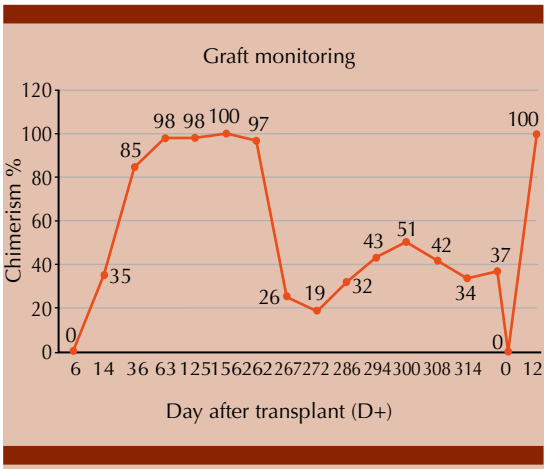

Figure 1. Dynamics of the chimerism after the two transplants.

outpatient Allo-HSCT with cells from the same blood relative was done in November 26th of 2015 achieving 100% of chimerism on D + 12; prophylactic drugs and low-dose of corticosteroids were administrated. In December 5th of 2015, patient presented a citomegalovirus (CMV) infection with IgM (+) titles of 1.07 AU/mL and IgG (+) > 250 AU/mL, treated with ganciclovir. Then, during aplastic phase of the second transplant, patient developed a rhinosinusal lesion that afterwards extended to soft palate. Causal agent was identified as *Mucor* sp. in December 13th of 2015 through fungal culture and skin lesion KOH exam **(Figure 2)**. Patient was admitted to Intensive Care Unit, where amphotericin B + posaconazol scheme was administrated. With partial response to antimycotic treatment and functional graft; patient presented sudden death for bronchospasm in January 3rd of 2016.

DISCUSSION

The present case shows a patient frankly predisposed to an infection for *Mucor* sp. First of all, MDS is a pathology that affects myeloid lineage; first line defense for spores eradication. On the other hand, therapies with corticosteroids, even though at low-dose, could have contributed in an

Figure 2. Picture of typical hyphae observed by optical microscopy using lactophenol cotton-blue stain on a culture sample taken from a white cotton candy colony; a rounded sporangium containing many rounded sporangiospores is shown.

important way to the immunosuppression during aplastic phase. Moreover, patient had a risk factor of T2DM accompanied by sever obesity that, although under a good glycemic control (such is this case), still being a predisposing characteristic. Despite its bad prognostic, it is not clear if this infection caused patient's dead, since there is not additional post-mortem data. Nonetheless, this scenario evidences an event that must to be considered in transplanted patients that present risk factors to avoid as far as possible this type of infection. Likewise, this report exhorts to work for improving prophylactic schemes and monitoring protocols that enhance survival of the patients. It is necessary to consider HSCT secondary mucormycosis, since albeit are rare, they represent a serious threat for patients in vulnerable situation. We suggest to follow this disease in management, predisposal factors and epidemiological data in Mexico, because real incidence of mucormicosis in patients with hematological malignancies after HSCT is until these days unknown and related bibliography is limited for this country, and are based in one center reports.

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