# Mucormycosis, COVID-19 and Acute Lymphoid Leukemia: Case Report

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**Research Article**

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# Abstract

*Introduction*: During the era of COVID-19, an increase has surged in the number of cases of mucormycosis; the use of high doses of steroids, and states of immunosuppression such as diabetes are the main related risk factors. In the treatment of acute leukemia, it is recommended to reduce the dose of chemotherapy, postponing highly myeloablative schemes and the use of caution with monoclonal antibodies.

*Case presentation*: We present the case of a patient (25 years-old male) with acute lymphoblastic leukemia and COVID-19 confirmed infection who developed rhino-cerebral mucormycosis during the induction stage.

*Conclusion:* In the age of COVID-19, taking samples through a nasal swab should be avoided in individuals with risk of infection from mucormycosis, such as diabetes, cancer, or individuals treated with high doses of steroids.


# Introduction

At the beginning of 2021, the critical moment of the pandemic was located in Latin America; countries like Mexico and Brazil recorded a significant rise in the mortality associated with individuals with recognized risk factors such as diabetes and hypertension [1, 2]. Then population with cancer was recognized as vulnerable since the first studies in China, requiring the modification of cytotoxic schemes, delaying surgeries and deferring doctor visits [3, 4]. In leukemia, it was recognized that the mortality associated with COVID-19 is potentially higher than 30%, limiting the efficacy of schemes with conventional chemotherapy or target therapies (venetoclax, FLT-3 inhibitors, IDH1/2 inhibitors), due to the delay in administration, in spite of the patients being asymptomatic [5]. In acute lymphoblastic leukemia, cooperative groups agree that highly immunosuppressor regimens should be used with caution, as well as the combination of monoclonal antibodies, and even transplant of hematopoietic progenitors should be delayed [6, 7]. With COVID-19, different bacterial (mainly *Staphylococcus*, *Escherichia coli*, *Pseudomonas aeruginosa*), viral (cytomegalovirus) and fungal infections are still fund among the main causes of complications related with treatment, and a polymerase chain reaction test should be applied in all cases with fever [8, 9]. Mucormycosis (zygomycosis) is a fungal infection caused by mucoral fungi (*Rhizopus oryzae* is the most common) that greatly affects immunocompromised individuals with high mortality [10]. Among the main risk factors for its development are neutropenia (60%) and acute leukemia (65%), with diagnosis from suspicion in more than half the cases and 40% performed post-mortem [11]. In our hospital, Bonifaz et al. recorded the experience of 35 years, reporting 214 cases of mucormycosis, the majority in patients with diabetes (76.6%), followed by individuals with hematological neoplasia (15.4%) [12]. Recently, a rapid rise in cases of mucormycosis was reported in individuals with COVID-19, associated mainly with uncontrolled diabetes mellitus (94%) or patients in critical state [13]. Sen et al. reported the series of six cases of patients with COVID-19 and mucormycosis that required antifungal treatment (liposomal amphotericin, posaconazol) and debridement treatment of necrotic tissue, with a

time of appearance of symptoms associated with mucormcosis of 15.6 ± 9.6 (3–42) days [14]. We present the case of a patient with acute lymphoblastic leukemia submitted to induction chemotherapy who presented COVID-19 infection and later nasal swab showed infection by rhino-cerebral mucormycosis.

# Case Presentation

Twenty-five year old male patient with history of insulin-dependent diabetes mellitus diagnosed since adolescence, in prolonged action insulin treatment with adequate adherence to treatment, entered to Department of Hematology for a study of leukocytes of 35 $x10^9$/L with 80% atypical lymphocytes, blood smear was performed, analysis of bone marrow identified acute lymphoblastic leukemia precursor B, habitual risk, negative Philadelphia chromosome, deciding to initiate induction stage with scheme of CALGB 10403. During pre-treatment with high doses of steroids, he developed lack of glycemic control, requiring an adjustment to insulin dose and receiving chemotherapy dose on day + 1 and + 8 (vincristine and doxorubicin), due to hyperglycemia, the use of asparaginase was deferred. On day + 13 of treatment, neutrophil count was 0.1 $x10^9$/L, he presented fever, and empirical antimicrobial therapy was initiated for febrile neutropenia. Due to the persistence of fever and oxygen desaturation, the polymerase chain reaction (PCR) test for SARS-CoV2 was requested, taking the sample by naso-pharingeal swab. Chemotherapy treatment was suspended until the fever improved. At 24 hrs from the swab, the patient showed rhinorrhea in the left nasal passage and pain, beginning with an increase in volume, and a tomographic study was taken, showing rhinosinusitis (Fig. 1a); his thorax X-ray showed data suggesting pneumonia (Fig. 1b), he continued antibiotic and antifungal treatment with fluconazole.

During follow-up, the patient persisted with fever, presenting swelling, erythema and intense pain at the left nasal rim (Fig. 1c), progressing rapidly in the following 48 hours. A culture was requested of nasal exudate, and direct visualization of fungi with KOH (potassium hydroxide) at 10% positive for *Rhizopus arrhizus.* (Figs. 2), our institution does not have other diagnostic tools for fungi such as PCR or sequencing methods. Treatment was begun based on amphotericin B; he persisted with fever and data of neurological deterioration, the tomograph after 5 days from the start of treatment showed cerebral affectation compatible with rhino-cerebral mucormycosis (Fig. 3). The patient showed progressive deterioration, requiring ventilator support and dying 7 days after start of symptoms. PCR results for SARS-CoV2 at 72 hrs from the swab were positive.

# Discussion

Infectious processes are among the main complications related with cancer treatment, especially with high-intensity chemotherapy. In leukemia, the use of high doses of steroids, especially during induction therapy, or comorbidities such as diabetes mellitus, are among the main risk factors for developing mucormycosis [15, 16]. During the last year, an increase has been observed in cases of mucormycosis, but associated with COVID-19, especially in areas such as India [17, 18]. There is a precedent in leukemia; Zurl et al. reported the case of a patient with acute myeloid leukemia, aged 53 years, who developed

pulmonary invasive mucormycosis; among his risk background were obesity (body mass index of 34 $kg/m^2$), depression, and being under prophylactic treatment with voriconazol 400 mg once a day, after induction on day + 54 of treatment, he developed a positive result for SARS CoV2 through nasopharyngeal swab; at 5 days he presented respiratory manifestations, entering on intensive care unit and diagnosed with *Rhizopus microsporus* infection through DNA sequencing methods [19]. Upon analyzing the different cases of COVID-19 characterized by pain and increase in volume of the orbital region [20–22], it has been agreed that the use of steroids is the main risk factor for developing rhino-cerebral mucormycosis. Other factors such as prolonged stay in an intensive care unit, ventilator support, pronation and finally the use of nasal points with high oxygen flow are factors that contribute to the colonization of fungal infections in individuals with COVID-19 [23]. Timely identification of manifestations suggesting mucormycosis (edema, pain, erythema, nasal flow), Access to diagnostic tools (cultures, polymerase chain reaction test, sequencing methods), and the timely start of antifungal therapies (liposomal amphotericin, voriconazol) are fundamental to avoid fulminant cases in patients with COVID-19 [24–26]. Finally, in our experience, individuals with leukemia, especially under immunosuppressor treatment with high doses of steroids, are susceptible to opportunist infections such as mucormycosis. In the age of COVID-19, other factors have been added, such as pronation, nasal flow with high-flow oxygen, and especially we must consider that techniques such as nasal swab are a critical factor for mechanical rupture and fungal colonization. Throughout the pandemic, complications have been described in the technique, including skull perforation, cerebrospinal fluid fistula or mucous lesion; knowing this, adequate training for taking samples is fundamental (including videos on YouTube), especially in individuals with risk factors such as cancer or diabetes [27, 28].

# Conclusions

In conclusion, individuals with lymphoblastic leukemia have an important risk of developing mucormycosis, and the taking of routine nasal samples may be deferred, or preferentially other sites such as the oral cavity should be used.

# Declarations

Funding: Not applicable.

Conflicts of interest/Competing interests: The authors declare no competing interests.

Ethics approval: All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. This data are part of the Project of “Leukemia and COVID-19”. It was approved by the ethics and research committees of the Hospital General de México (DI/20/204/04/41) and the Hospital Regional de Alta Especialidad Ixtapaluca (NR-13-2020). The study was registered in ClinicalTrials.gov (NCT04745416).

Consent to participate: Additional informed consent was obtained from the patient for whom identifying information is included in this article.

Consent for publication: A consent form was signed by the patient giving consent for use of images in publication, a copy of which is filed with the patient's case notes.

Availability of data and material: Not applicable.

Code availability: Not applicable.

Authors' contributions: Dr. Edgar Cordero clinically managed the case and contributed in manuscript writing; Dr. Carlos Martinez-Murillo wrote the manuscript, and did literature search; Dr. Gilberto Barranco-Lampón clinically managed the case and contributed in manuscript writing; Dra. Itsel Arias-Castro supplied the acquisition of data and biological samples, analysis, and contributed in manuscript writing. Dr. Adrián Santoyo-Sánchez contributed in compiling the manuscript and submission. Dr. Christian O. Ramos-Peñafiel revised the manuscript critically for important intellectual content and gave final approval of the version to be submitted; All authors read, discussed the results, and approved the final manuscript.

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# Figures

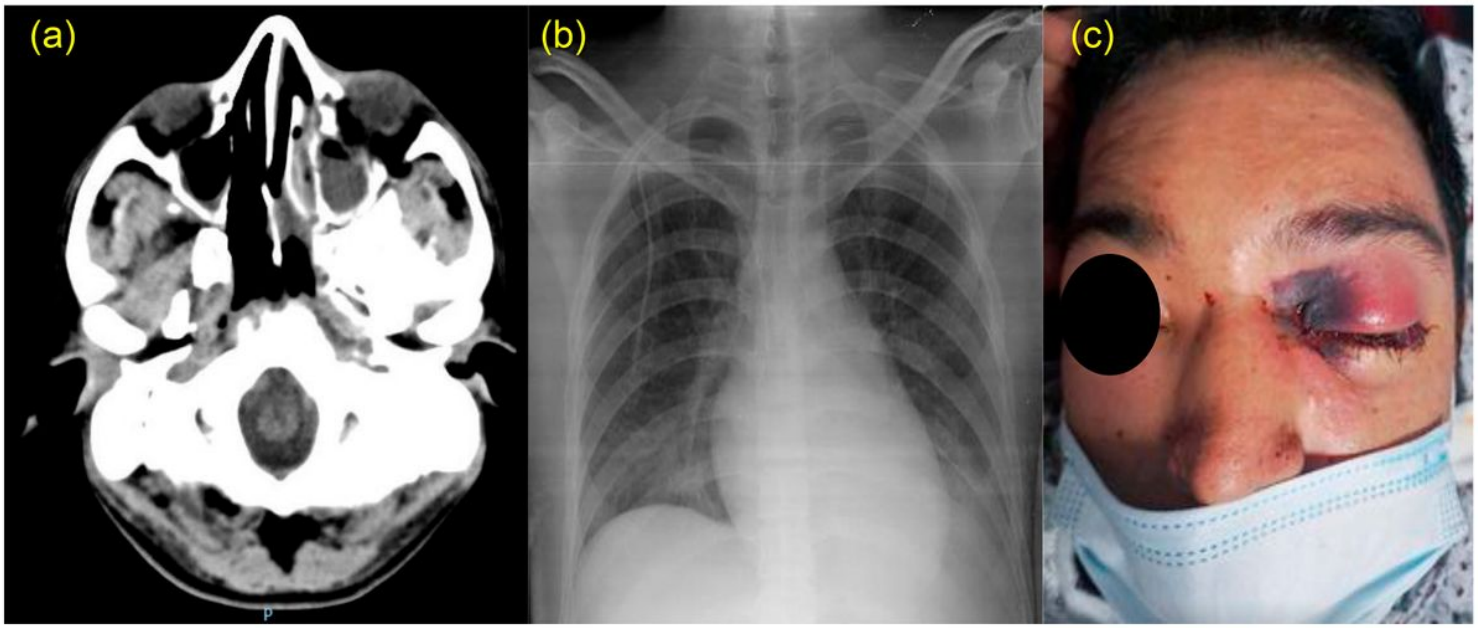


**Figure 1**

(a) Erythematous lesion on the edge of the left nostril, with erythema and ecchymosis. (b) Tomographic occupative lesion study of left nasal cavity. (c) X-ray of thorax with changes associated with bilateral pneumonia.

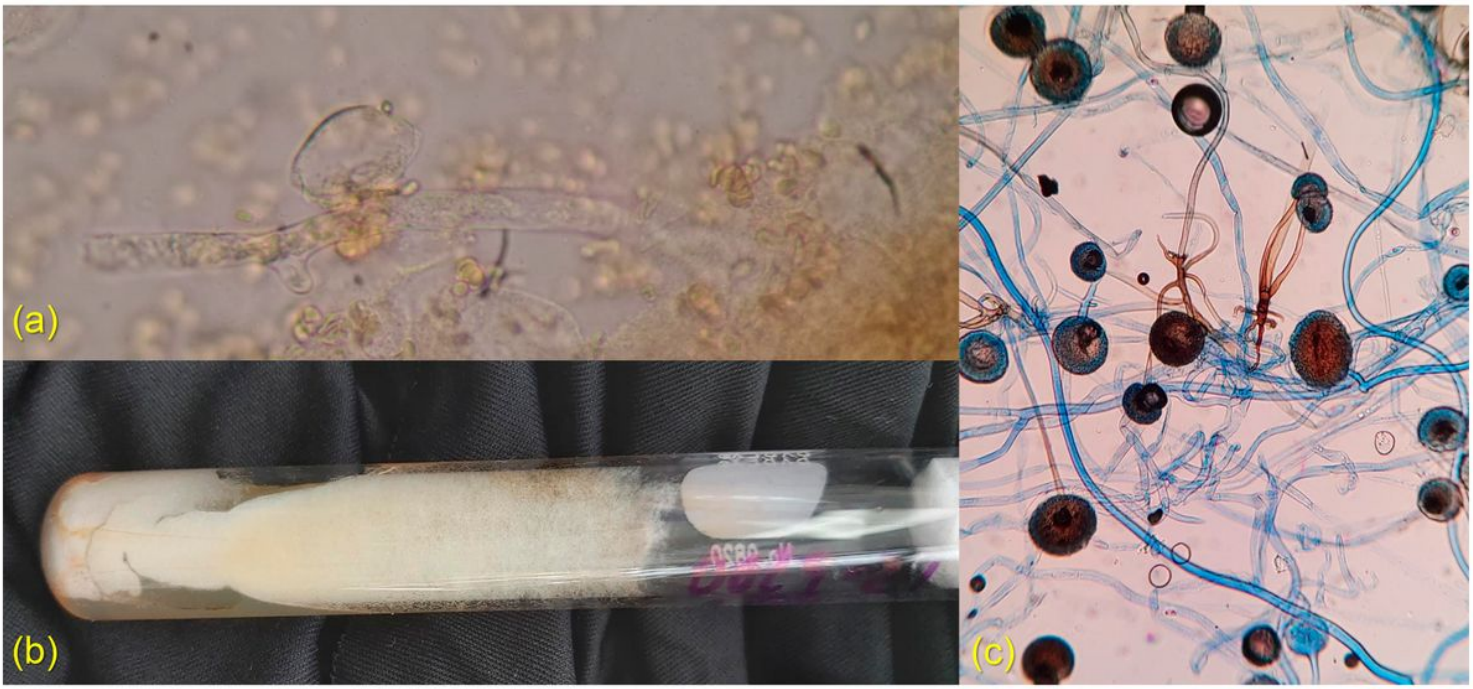


**Figure 2**

(a) Sinocytic hyaline hypha, dichotomized, thick in sample tissue under direct visualization (400x) with KOH at 10%. (b) Development of white cottony fungus with dark grey surface without diffusible pigment in Sabouraud dextrose agar at 48 hrs of incubation at 30°C. (c) Sporangium and sporangiospores in culture of Rhizopus arrhizus, with rhizoids (Lactophenol cotton blue stain, 400x)

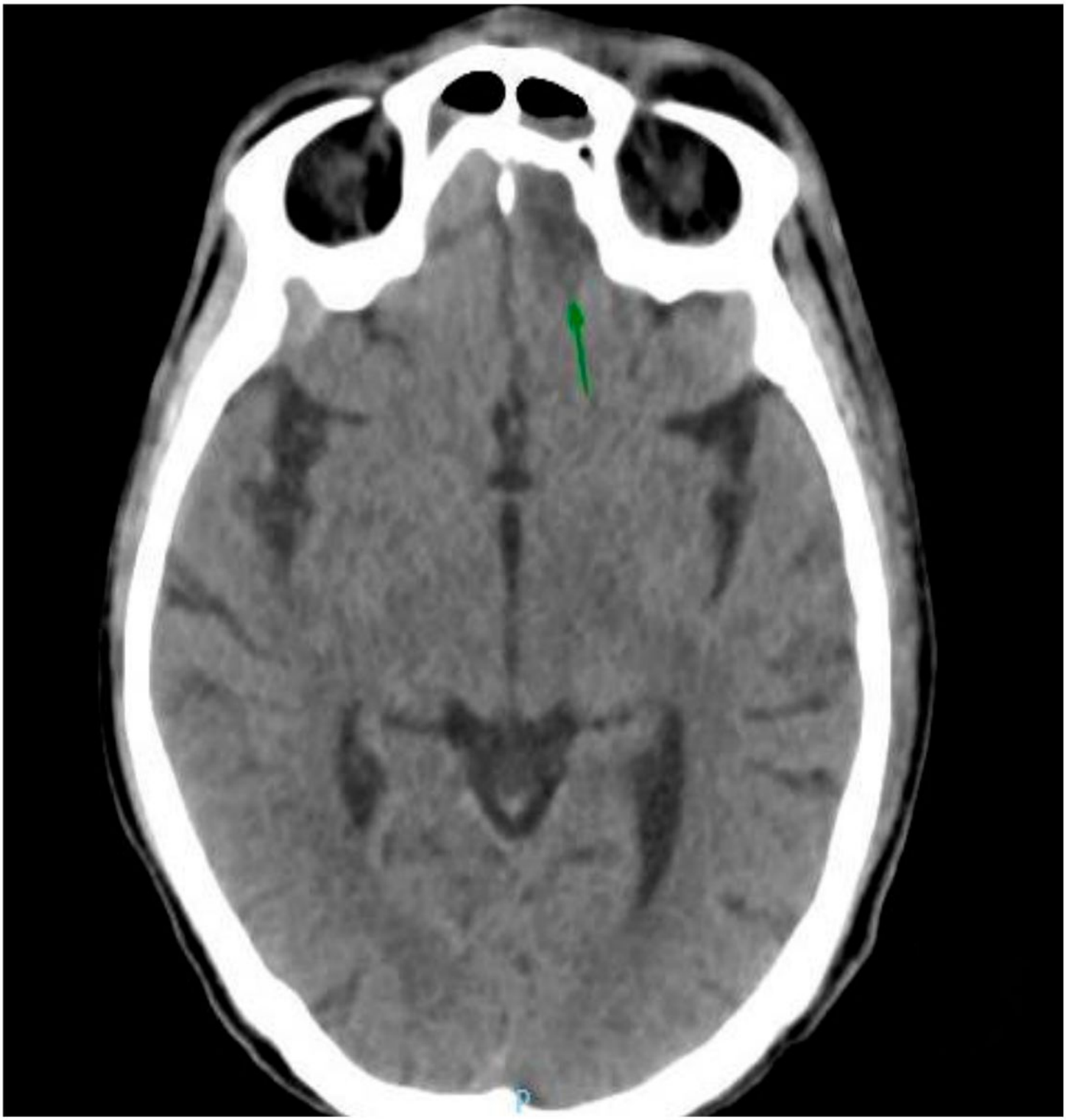

**Figure 3**

Tomographic study with evidence of rhino-cerebral mucormycosis (green arrow)

## Supplementary Files

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- CAREchecklistRamosP.pdf