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CLINICAL CASE

Disseminated mucormycosis in a child with acute lymphoblastic leukemia: autopsy findings

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Abstract

Background: *Mucormycosis is a rare infection caused by ubiquitous fungi of the Mucorales order that mainly affects immunocompromised patients. These fungi have an important tropism for blood vessels that allows them to spread rapidly and cause thromboembolic events.* **Case report:** *We present a case of an 8-year-old male patient diagnosed with acute lymphoblastic leukemia treated with chemotherapy. He presented icteric syndrome, hepato-splenomegaly, and data of intestinal obstruction. Although he underwent intestinal resection, he did not improve and died. The autopsy identified disseminated mucormycosis involving the brain, lungs, esophagus, small intestine, colon, and pancreas.* **Conclusions:** *Hematological neoplastic diseases and their treatment are important risk factors for developing infections by opportunistic microorganisms such as mucormycosis. Early diagnosis and adequate treatment are essential due to their intrinsic difficulty and the high mortality rate of these cases.*

Keywords: *Lymphoblastic leukemia. Mucormycosis. Neutropenia. Autopsy. Amphotericin B.*

Mucormicosis diseminada en un paciente pediátrico con leucemia linfoblástica aguda: hallazgos de la autopsia

Resumen

Introducción: *La mucormicosis es una infección poco frecuente causada por hongos ubicuos del orden de los Mucorales que afecta principalmente a pacientes inmunocomprometidos. Estos hongos poseen un importante tropismo por vasos sanguíneos que les permite diseminarse rápidamente y provocar lesiones trombo-embólicas.* **Caso clínico:** *Se presenta el caso de un paciente de sexo masculino de 8 años con diagnóstico de leucemia linfoblástica aguda tratada con quimioterapia. Presentó síndrome ictérico, hepato-esplenomegalia y datos de obstrucción intestinal. A pesar de que fue sometido a resección intestinal, no presentó mejoría y falleció. En la autopsia se identificó mucormicosis diseminada con afección de cerebro, pulmones, esófago, intestino delgado, colon y páncreas.* **Conclusiones***: Las enfermedades neoplásicas hematológicas y su tratamiento son importantes factores de riesgo para el desarrollo de infecciones por microorganismos oportunistas como la mucormicosis. El diagnóstico temprano y adecuado tratamiento son importantes debido a la dificultad intrínseca de los mismos y la alta tasa de mortalidad de estos casos.*

Palabras clave: *Leucemia linfoblástica. Mucormicosis. Neutropenia. Autopsia. Anfotericina B.*

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Introduction

Mucormycosis is an infection caused by saprophytic fungi of the *Mucorales* order that mainly affect immunocompromised individuals. Children with hematological malignancies undergoing chemotherapy treatments involving immunity are among the highest-risk groups. When the index of suspicion is low, this diagnosis can go unnoticed, which has severe consequences since the mortality rate in patients who develop the disseminated disease can be as high as 100%[1-3].

Clinical case

We describe the case of an 8-year-old male patient diagnosed with acute lymphoblastic leukemia, treated with methotrexate, mercaptopurine, folinic acid, cytarabine, and hydrocortisone.

One year after diagnosis, he developed jaundice, mucositis of the oral cavity, and hepatosplenomegaly while receiving third-line treatment with mitoxantrone and cytarabine. Abdominal examination revealed hepatomegaly 10 cm below the costal margin. No abnormal data were detected on cardiopulmonary physical examination.

Laboratory test results indicated hyperglycemia (435 mg/dL), leukopenia ($3.7x10^3$/uL) with neutropenia (24.2%), anemia (8.3 g/dL), thrombocytopenia ($10x10^3$/uL), elevated liver enzymes (aspartate aminotransferase 219 U/L, alanine aminotransferase 49 U/L), hyperbilirubinemia (direct 10.03 mg/dL, indirect 8.23 mg/dL), and increased lactate dehydrogenase (3870 U/L).

The patient presented with epistaxis, hand-foot syndrome secondary to cytarabine, fever, and abdominal pain. He was initially treated with ceftazidime-amikacin. However, after 15 days with persistent fever and neutropenia, treatment was changed to imipenem-amikacin. Twenty days after hospitalization, the patient presented intestinal occlusion data.

An abdominal X-ray showed a fixed loop of the small bowel, so neutropenic colitis was suspected. An abdominal ultrasound reported left hemi-colon with data related to probable neutropenic colitis. The patient showed signs of intestinal occlusion, so an exploratory laparotomy was performed. A 21 cm long segment of the ileum with ischemic necrosis was identified and resected during surgery. Subsequently, the patient evolved poorly and presented systemic inflammatory response syndrome and respiratory failure data leading to death. The final clinical diagnoses were intestinal occlusion due to neutropenic colitis and acute refractory leukemia.

The autopsy revealed diffuse, poorly demarcated necrotic and hemorrhagic lesions in the lungs, along the gastrointestinal tract, mainly in the esophagus, stomach, small intestine, colon, and central nervous system. In addition, thromboembolic lesions completely obstructing the vascular lumen were observed in vessels near the pulmonary hilum, predominantly on the right side (Figure 1).

A disseminated thromboembolic disease was identified microscopically, mainly in the organs showing macroscopic lesions. Within the vascular lumina, abundant fungal microorganisms with irregular “ribbon” shaped hyphae, pauci-septate, branched predominantly at right angles and with optically empty centers, compatible with mucormycosis, were detected. These microorganisms were also found in the parenchyma adjacent to the occluded vessels, accompanied by extensive ischemic necrosis (Figures 2 and 3).

Bone marrow studies by post-mortem cytologic smears, definitive sections, and immunohistochemistry revealed persistent lymphoblastic leukemia. As additional findings, the heart showed multiple dystrophic calcifications and liver steatohepatitis.

Discussion

Mucormycosis is a rare infection caused by naturally ubiquitous saprophytic fungi of the order *Mucorales*[1] and is characterized by a rapid and aggressive progression, affecting immunocompromised individuals[2]. It predominates in males (58-64% of cases), with a mean age between 5-10 years, consistent with this case. The most frequently identified genera are *Rhizopus spp.* (22-44% of cases), *Mucor spp.* (11-15% of cases) and *Lichtheimia spp.*[1,3-5].

Frequently, the diseases underlying this infection are hematologic malignancies. These conditions are associated with 39-46% of cases, with neutropenia being the leading risk factor in this group of patients, also present in this case[1,5]. About 93% of these neoplasms correspond to acute leukemias[4,6]. Other risk factors include children undergoing hematopoietic stem cell transplantation, premature infants, and diabetes mellitus[1].

In most cases, the fungus enters the body through the respiratory tract[4,6]. Thus, the most frequent clinical presentation is rhinosinusitis (28% of cases) and pulmonary involvement (19% of cases)[5], with dissemination occurring in 24-38.1% of cases. Although less frequent (17% of cases),[1] gastrointestinal presentation was detected in this case.

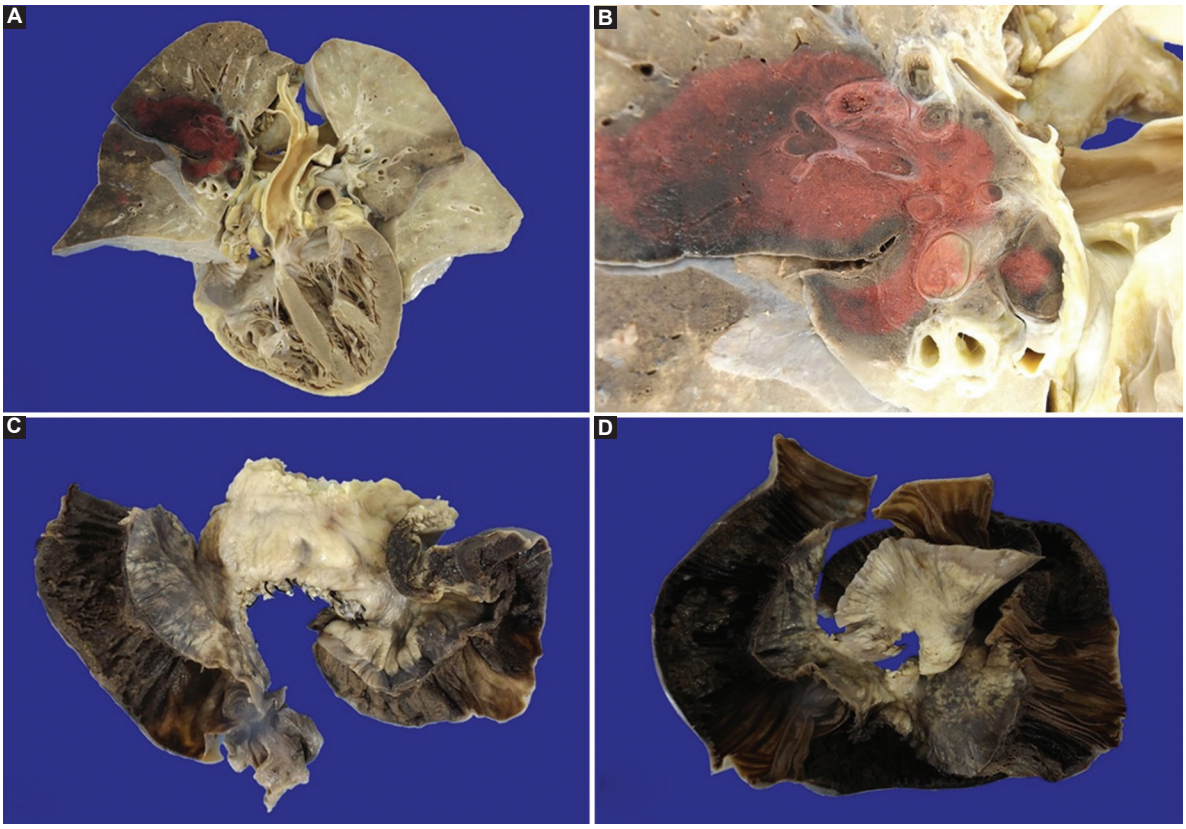

Figure 1. Disseminated mucormycosis. **A:** cardiopulmonary block with necrosis and hemorrhagic lesions in the right lung. **B:** detail of blood vessels near the pulmonary hilum completely obstructed by thromboembolic lesions with necrosis of the adjacent parenchyma. **C:** small bowel segment in the region of the previous surgical resection. The intestinal loop and part of the mesentery with necrosis and hemorrhagic aspect are observed. **D:** the regions of the intestine distal to the resection site also show transmural ischemic-hemorrhagic enteritis with mesentery involvement.

The pulmonary lesions identified in the autopsy study might suggest that this was the primary focus of infection. However, it should be noted that gastrointestinal symptoms predominated-without apparent respiratory involvement-during the clinical course. This could indicate that the pulmonary lesions correspond to an embolism developed at the end of the clinical picture that could have contributed significantly to the patient's death.

One of the most important characteristics of *Mucorales* is their marked vascular tropism, which facilitates hematogenous dissemination and vascular thrombosis, causing lesions with extensive tissue necrosis[7]. This scenario hinders the arrival of leukocytes to the site of infection and the penetration of drugs into the tissues, complicating treatment[8].

Although a histological examination is preferable, biopsy procedures may be limited by the patient's hemodynamic conditions or platelet levels[4]. Diagnosis is also complicated as cultures are not very sensitive due to the friability of the hyphae; this method is positive in only one-third of cases. Tests for (1-3)-beta-D-glucan and galactomannan are useless, as these fungi lack these polysaccharides in their walls[7].

Microscopically, these fungi are characterized by non-septate or pauci-septate hyphae with a twisted or "ribbon-like" appearance, branching at right angles from the progenitor hyphae[1]. These features allow a presumptive differential diagnosis between other hyalohyphomycoses and phaeohyphomycoses[4]. Other reliable techniques for diagnosis are PCR (polymerase chain reaction)[1] and, although less available, next-generation metagenomic sequencing techniques that can be performed on peripheral blood, cerebrospinal fluid, and bronchioalveolar lavage fluid[9]. Proper diagnosis is of utmost importance, as misdiagnosis or empirical treatment delays appropriate treatment with ineffective clinical outcomes[10].

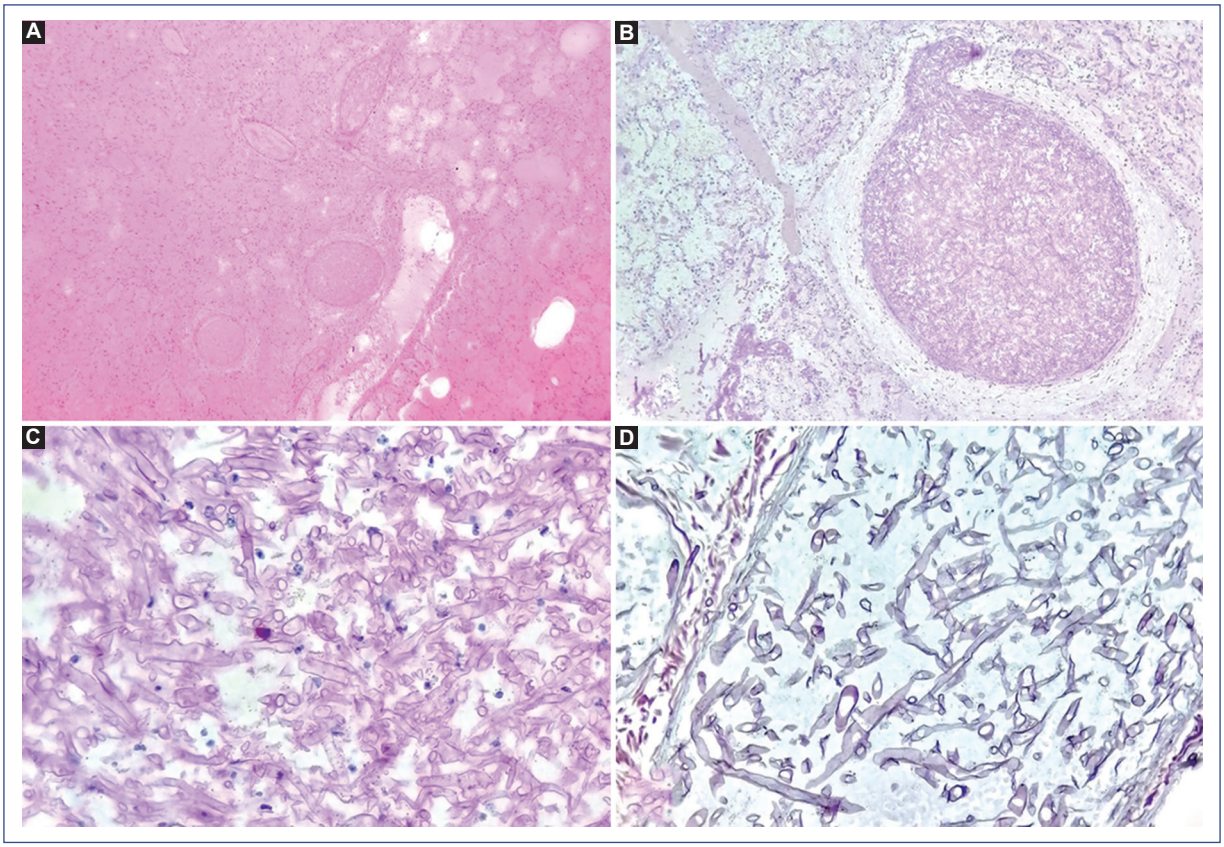

Figure 2. Disseminated mucormycosis. **A:** histological section of the lung with total loss of architecture due to extensive ischemic necrosis, with complete vascular occlusion (hematoxylin and eosin staining, 40x). **B:** blood vessels are entirely occluded by mycotic thrombi (periodic acid Schiff staining, 100x). **C:** the morphology of the fungi corresponds to irregular, pauci-septate, branched, "ribbon" shaped hyphae (periodic acid Schiff staining, 400x). **D:** argentic impregnation staining identifies the above characteristics (Grocott staining, 400x).

Confirmation of mucormycosis diagnosis does not rule out the presence of other microorganisms: co-infection with *Aspergillus* and other bacterial infections has been described in 27-48.4% of cases[11,12]. This important issue should be considered when establishing treatment.

The cornerstones of treatment are antifungal therapy with liposomal amphotericin B and surgical debridement[2,4,7]. However, the overall mortality rate is 50-100%, considerably higher than that of *Aspergillus* (between 20-50%)[7]. As shown in this case, the disseminated form generally has the worst prognosis, with 100% mortality rates[3,4]. Regardless, outcomes can be improved with timely diagnosis and aggressive treatment[2,3,5].

Although the most critical complication of antineoplastic treatment was mucormycosis, we identified other complications in this case. The patient presented hand-foot syndrome or palmar-plantar erythrodysesthesia syndrome, which has been described as secondary to the administration of high doses of cytarabine predominantly. However, it has also been reported in cases of methotrexate use[13], both drugs used in this patient. The autopsy identified steatohepatitis, which has also been attributed to administering drugs that induce hepatotoxic lesions, such as methotrexate[14]. The multiple dystrophic calcifications in the heart were associated with various factors, such as infections, inflammatory conditions, or cytotoxic drugs[15], all present in this patient.

Mucormycosis is a rare infection that mainly affects immunocompromised patients, such as those diagnosed with acute leukemia and treated with chemotherapy who present neutropenia. This case report highlights the importance of considering the diagnosis of mucormycosis in the presence of persistent fever in patients with risk factors since its timely diagnosis will allow adequate treatment and decrease the high mortality rate.

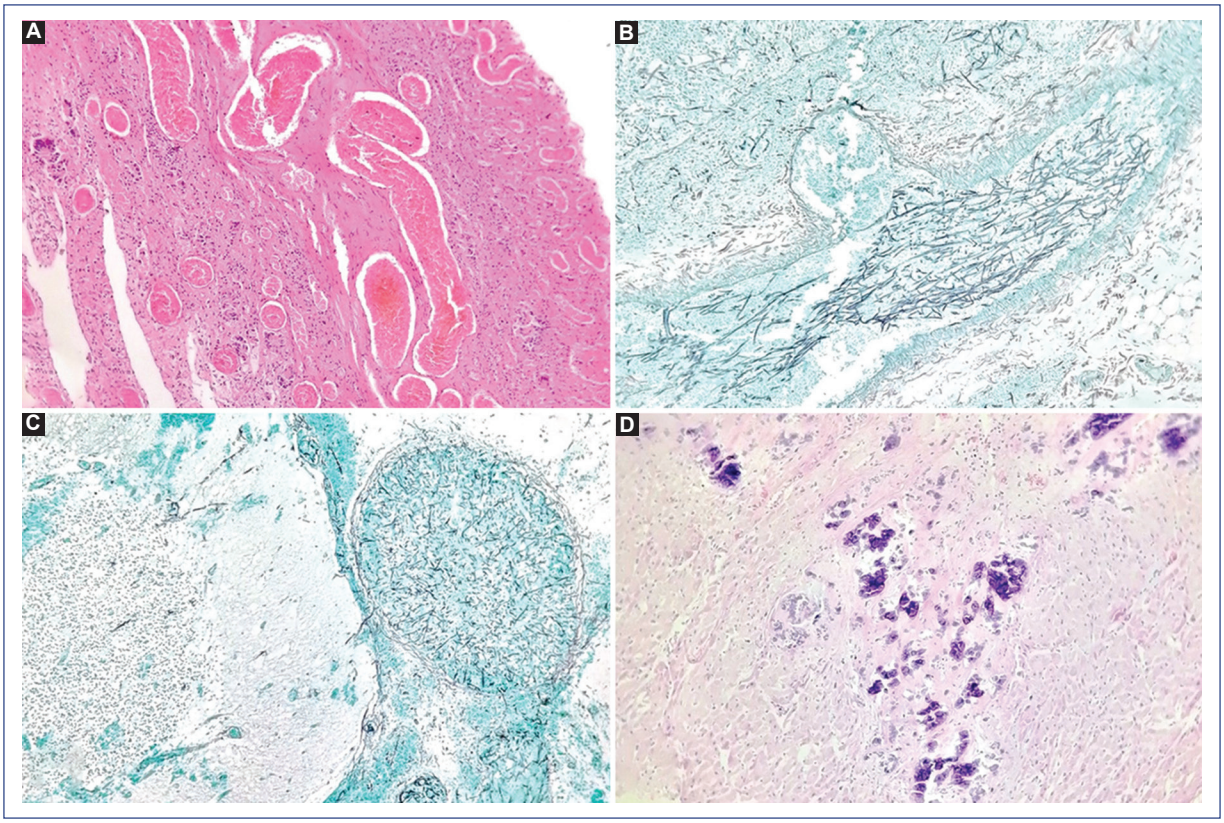

Figure 3. Disseminated mucormycosis. **A:** mycotic thrombi completely occlude the mesentery vessels, with extensive ischemic necrosis (hematoxylin and eosin staining, 40x). **B:** in the brain, mycotic thrombi are also identified in a secondary pseudo-aneurysm (Grocott staining, 100x). **C:** in the cerebellum, fungal thrombi are identified, some migrating through the vascular wall into the cerebellar cortex (Grocott staining, 100x). **D:** in the heart, multiple dystrophic calcifications are observed between muscle fibers (hematoxylin and eosin staining, 100x).

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflicts of interest.

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