

Artículo original

Intestinal disseminated zygomycosis, associated with hyperinfection syndrome caused by *Strongyloides stercoralis*

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Resumen

Se presenta el caso de un niño de 11 años de edad, del estado de Guerrero. El antecedente previo a su ingreso a este Instituto era de una laparotomía exploradora y probable linfoma no Hodgkin. A su ingreso se realizó otra laparotomía exploradora y biopsia de tejido intestinal para estudio histopatológico y examen directo en fresco aclarado con hidróxido de potasio de macerado de tejido intestinal. Se hallaron abundantes hifas hialinas, aseptadas, irregulares, gruesas, dicotomizadas; se diagnosticó zigomicosis gastrointestinal. En el macerado intestinal se hizo examen de sedimentación por el método de Ritchie y se encontraron abundantes larvas de *Strongyloides stercoralis*. Se le administraron anfotericina B, albendazol e ivermectina. El paciente falleció pese al tratamiento. En la autopsia se confirmaron los diagnósticos clínicos. Este es el sexto caso descrito en la literatura con diagnóstico premortem de zigomicosis diseminada.

Palabras clave: Zigomicosis diseminada, síndrome de hiperinfección, *Strongyloides stercoralis*, larvas, método de Ritchie.

Introduction

Zygomycosis (Phycomycosis) embraces one group of opportunistic fungi infections due of Zygomycetes class, Mucorales order. Class members are true fungi constituted by 10 to 30 um diameter hyphae pauciseptated or unseptated.

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Abstract

An eleven year old boy from the state of Guerrero, Mexico, with the history of an exploratory laparotomy and probable non-Hodgkin lymphoma is presented. On admission to the Instituto Nacional de Pediatría (National Institute of Pediatrics) another exploratory laparotomy was performed and a biopsy of intestinal tissue was taken. The histopathological study, by direct examination of macerated intestinal tissue, cleared with potassium hydroxide reported abundant hyalin, irregular, unseptated, thick, dichotomized hyphae. The diagnosis was gastrointestinal zygomycosis. With the macerated intestinal tissue a sedimentation examination with Ritchie's method was done; several *Strongyloides stercoralis* larvae were found. He was treated with amphotericin B, albendazole and ivermectin. The patient died despite the medication. At autopsy the clinical and laboratory diagnosis was confirmed. This is the sixth case reported with premortem diagnosis of disseminated zygomycosis.

Key words: Disseminated zygomycosis, hyperinfection syndrome, *Strongyloides stercoralis*, larvae, Ritchie's method.

The most important pathogenic genera known are *Mucor*, *Rhizopus* and *Absidia*. They can be found in plants, ground, rotten fruits and dead animal tissues. It has been documented as saprophytic in 3% of humans, but in the presence of a disease, it is an opportunistic fatal infection.^{1,2} This infection is observed in immunocompromised patients, after chemotherapy, bone marrow transplant, use of steroids, renal failure, diabetics with keto-acidosis and premature babies; some cases are seen after local trauma associated with the use of elastic or adhesive bands.³⁻⁵ It affects patients with malnutrition and pre-existing intestinal ulcers.⁶

Zygomycosis is characterized by vascular lesions with thrombosis, hemorrhage and infarction. Clinical presentation varies considerably and is categorized into rhinocerebral, pulmonary, disseminated, gastrointestinal, cutaneous and miscellaneous.³

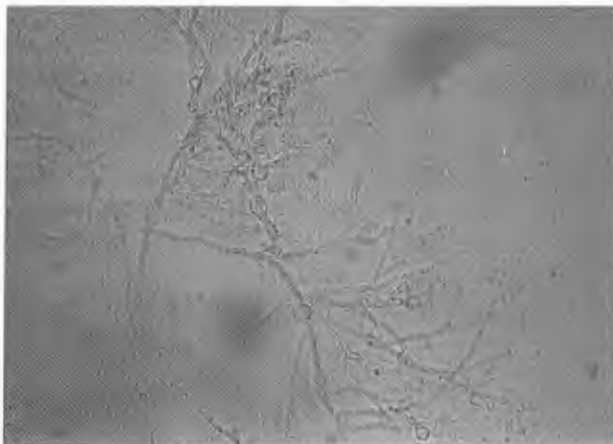


Figure 1. Macerated intestinal tissue cleared with potassium hydroxide showing broad, dicotomized zygomyces micelia. Clear field microscopy 400X.

To our knowledge this is the sixth case in the English literature of disseminated Zygomycosis diagnosed pre-mortem. In addition the patient suffered hyperinfection syndrome by *Strongyloides stercoralis*.

Case report

An 11 year-old boy from Guerrero, Mexico in extreme poverty had a history of acute appendicitis resolved 4 months before in a local clinic with no pathologic specimen analysis. A second laparotomy was necessary three months later because of an intestinal obstruction. The presence of retroperitoneal enlarged matted lymph nodes with mesenteric "invasion" suggested possible non-Hodgkin lymphoma whereupon he was referred to the National Institute of Pediatrics (Instituto Nacional de Pediatría). Physical examination on admission: body weight of 23.5 kg, length 132 cm. According to Waterlow's classification, the patient had a second grade malnutrition with a weight deficit of 38.7%. Intestinal obstruction was present. A complete blood count revealed severe anemia: hemoglobin, 9.6 g/dL, hematocrit, 30; leukocytosis with 35,800/mm³; lymphocytes 32%; segmented 87%. A third laparotomy was performed; bridolysis and mesentery biopsy were done. Antibiotic therapy with ampicilin, metronidazol and amikacin was initiated. Admission to the intensive care unit was necessary because of a blood volume loss of 1,010 cc. Histopathologic study of a mesenteric mass showed granulomata inflammation with eosinophilia, tissue necrosis, arterial and venous thrombosis. Direct examination of mesenteric tissue, cleared with potassium hydroxide showed abundant hyaline, un-

septated and irregular wide hyphae. Intestinal Zygomycosis was diagnosed and a retrospective biopsy study revealed the same pleomorphic hyphae with Charcot-Leyden crystals and Splendore phenomena. (Figure 1)

Gastrostomy, jejunostomy with duodenal exclusion and resection of one meter of jejunum were done because of the presence of patchy necrosis. A few hours after surgery, active bleeding of surgical incisions and drains were noted. Emergency surgery disclosed a bleeding mesenteric vessel and intestinal layer bleeding that required packing. Disseminated intravascular coagulopathy was treated with fibrinogen 70 mg/dL, PT 23%, monomers and positive dimmer. Examination of the intestine fragment sediment by the Ritchie method showed abundant rhabditoid larvae of *Strongyloides stercoralis*, *Toxocara canis*; ELISA test was negative. (Figure 2)

Albendazol 400 mg every 24 h for 5 days and ivermectine, 200 mcg/kg/day for two days were given. The patient died four days later following a severe unpacked hemorrhage from an extensive necrosis involving the stomach and the entire intestine.

Autopsy findings: Isolated *Strongyloides stercoralis* larvae were found in the small intestine, the liver and in the peripancreatic tissue. Angioinvasive zygomycosis was present in the abdomen and the lungs with extensive thrombi in the abdominal aorta and its main branches: celiac, mesenteric and renal arteries. There was extensive ischemic necrosis in the stomach, small intestine and colon; focal necroses in liver, spleen, left kidney and adrenals were present with bacterial proliferation (gram negative bacilli)

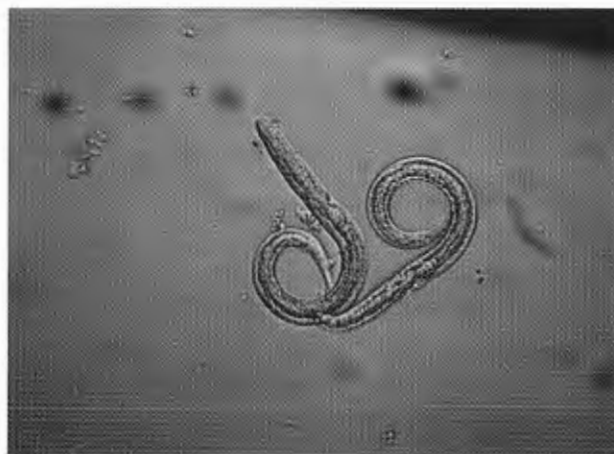


Figure 2. Sediment microscopic examination. Two rhabditoid larvae of *Strongyloides stercoralis* are observed.

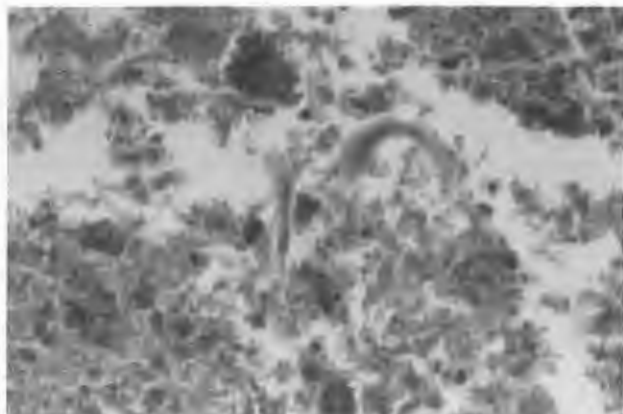


Figure 3. Strongyloides larvae in a mesenteric tumor. Adjacent optic clear structures are consistent with unseptated hyphae. (PAS stain, 40X).

in the gastrointestinal tract, kidneys and adrenal glands. Acute and chronic pancreatitis with extensive hemorrhage was also observed. (Figures 3, 4a, 4b, 5).

Discussion

Disseminated Zygomycosis involves mainly liver, spleen, kidneys, heart, duodenum, pancreas and stomach. Pre-mortem diagnosis is extremely rare because of the non-specific clinical features and the difficulty to obtain a biopsy and cultures. There are six previously published cases to our knowledge.

Direct examination of necrotic tissue cleared with potassium hydroxide is a reliable test to show mycelia in suspected cases of fungus disease.

High mortality in these patients is due to the underlying disease and the severity of the fungus infection. A review of 26 cases of disseminated Zygomycosis of the literature in 41 years indicates that pre-mortem diagnosis was done in five cases. Only one patient treated with the use of amphotericin B, granulocyte colony-stimulating factor and surgical removal of a lung lesion survived.⁷

On the other hand, there are cases of hyperinfection or of disseminated *Strongyloides stercoralis* associated with altered T-cell lymphocyte function as in AIDS, renal transplant, or patients under steroid treatment. Clinical features depend on the infectious events originated by the penetration of *Strongyloides* larvae transporting gram negative bacteria to the bloodstream thus causing sepsis, lung, brain or liver abscess, pneumonia and meningitis. These manifestations are preceded by a history of chronic



Figure 4a. Cross section of the abdominal aorta with thrombi.

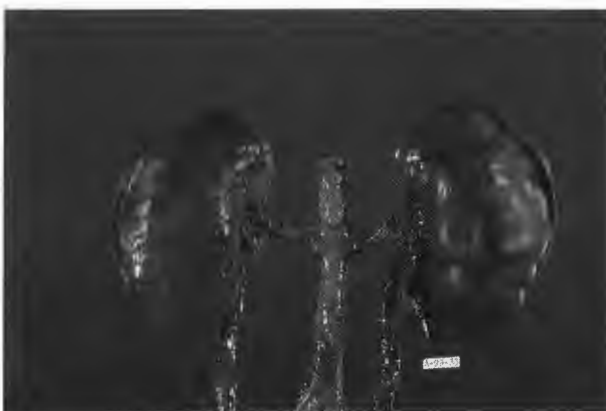


Figure 4b. Bilateral renal infarcts secondary to arterial thrombi.

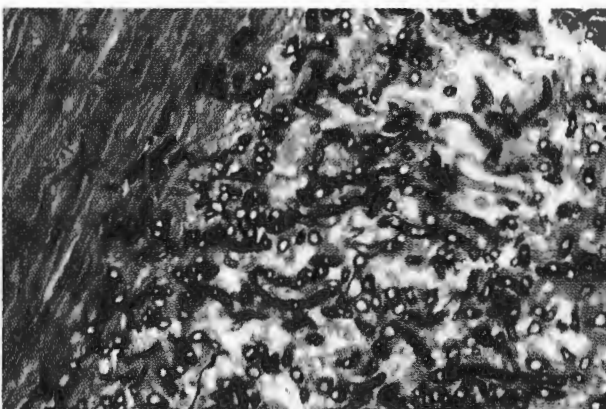


Figure 5. Thrombi composed of numerous hyphae with optic clear zones consistent with Zygomycetes. Note angioinvasive character of hyphae in the left side (Grocott's methenamine silver stain, 25X).

abdominal pain and diarrhea. This condition is fatal in about 75% of the cases, even when using specific therapy.^{8,9} Our findings suggest that there is a synergism between *Strongyloides* larvae and zygomycetes hyphae.

Eosinophilia is generally absent in these patients. Chest X-rays may show interstitial and alveolar bilateral infiltrate. The diagnosis is suspected in severe immunocompromised patients when *Strongyloides* larvae are found in bronchial aspirate or in a stool examination during a septic episode. Baerman's method is a simple and sensitive test in cases of asymptomatic strongyloidiasis. In the syndrome of hyperinfection elimination of larvae may be scanty because of the intense process of severe autoinfection.^{10,11}

The present case posed a diagnostic problem. A surgical approach was contemplated because a neoplastic process was suspected; however the abdominal chronic granulomatous inflammation with numerous eosinophils discarded that diagnosis and a parasite invasion was a possibility. It was decided to do a direct examination of intestinal macerated tissue, cleared with potassium hydroxide to look for opportunistic fungus as *Aspergillus* and Zygomycetes and by the sediment study with Ritchie method to investigate *S. stercoralis* and ELISA for *Toxocara*.

Elective treatment for Zygomycosis continues to be amphotericin B since other antimycotics such as triazoles have not been effective. In the hyperinfection with *Strongyloides* syndrome the elective treatment is ivermectin.¹¹

Gastrointestinal Zygomycosis with or without dissemination, and hyperinfection syndrome by *Strongyloides*

should be considered in the differential diagnosis in patients with severe malnutrition or in those immunocompromised with gastrointestinal symptoms and systemic involvement.

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