Invasive gastrointestinal aspergillosis in an immunocompromised host

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Invasive Aspergillosis (IA) is a common opportunistic infection in immunocompromised individuals. The IA is an important cause of morbidity and mortality in patients with hematological malignancies and it is particularly common during neutropenic episodes following anticancer chemotherapy.[1] While pulmonary aspergillosis involvement is common, gastrointestinal (GI) aspergillosis infection with clinical manifestation is rare. Gastrointestinal aspergillosis is usually seen in the most severely immunocompromised patients, especially those with prolonged, severe neutropenia. We present a case as an invasive gastrointestinal aspergillosis confused with graft-versus-host disease (GVHD) in post bone marrow transplant patient and brief review of the literature of GI aspergillosis.

A 16 year-old male presented to the GI service with hematemesis and bloody diarrhea. He was initially diagnosed with standard risk acute lymphoblastic leukemia (L-1 morphology) in March 1994 at the age of 5 years. He had central nervous system involvement. He was treated with standard chemotherapy (Children's Cancer Group 1992) from March 1994 to May 1997. He initially responded to treatment, but his disease relapsed twice in 1998 and 2002. He received a 4-drug re-induction chemotherapy and a reduced consolidation phase of high dose Ara-C/ Idarubicin with resultant clinical remission. A bone marrow transplant from a matched unrelated donor was performed in May 2002. He relapsed in May 2004 and was treated with a 4-drug re-induction. He subsequently received donor lymphocyte infusions on March 2nd, April 7th, and May 25th, 2005. Following the 3rd lymphocyte infusion, he developed diarrhea, a skin rash and conjugated hyperbilirubinemia with transaminase and Gamma-Glutamyl Transpeptidase elevation. Examination of the skin revealed a diffuse maculopapular rash with exfoliation. He was treated with IV cyclosporine and high dose prednisone (2 then 4 mg/kg) for presumed GVHD with involvement of skin, gut, and liver. Infliximab was added because of worsening symptoms and rising conjugated bilirubin and transaminase levels. Gastroenterology service was consulted because of worsening symptoms, now with bloody diarrhea and minor hematemesis. Endoscopic examination was not performed at the time because of an ongoing coagulopathy, thrombocytopenia, and neutropenia. A skin biopsy was carried out, which demonstrated aspergillus hyphae, but without features of GVHD. Caspofungin and voriconazole were started and the immunosuppressive agents were discontinued. To definitively exclude GVHD and infectious etiologies in the GI tract, upper GI endoscopy and sigmoidoscopy were performed on August 4th, 2005. The upper GI endoscopy revealed multiple erosions in the distal esophagus and the sigmoidoscopy revealed loss of vascular markings, mucosal edema and friability in the sigmoid colon and rectum. Biopsies showed no evidence of GVHD and aspergillus was not detected. The CT scan of the head, chest, abdomen and pelvis revealed diffuse fungal balls, consistent with disseminated aspergillosis. The patients passed away on 11th of August 2005. Postmortem examination revealed multiple yellow nodular lesions in both the left and the right lobes of the liver, measuring 0.1-1.3 cm in maximum dimension. A necrotic center is noted in the larger lesions. There is evidence of parenchymal congestion and cholestasis. The small bowel mucosa is hemorrhagic, and a cast of clotted blood is present in the lumen. Multiple mucosal lesions are present throughout the small and the large bowel, measuring up to 0.5 cm in maximum dimension. Microscopic examination of the lesions in the small and large bowel (**Figure 1**) revealed septated fungal hyphae branching in an acute angle, the morphology of which is consistent with aspergillus.

Invasive pulmonary aspergillosis is a common opportunistic infection in immunocompromised individuals, while GI aspergillosis involvement is rare. Over the past 20 years, invasive aspergillosis

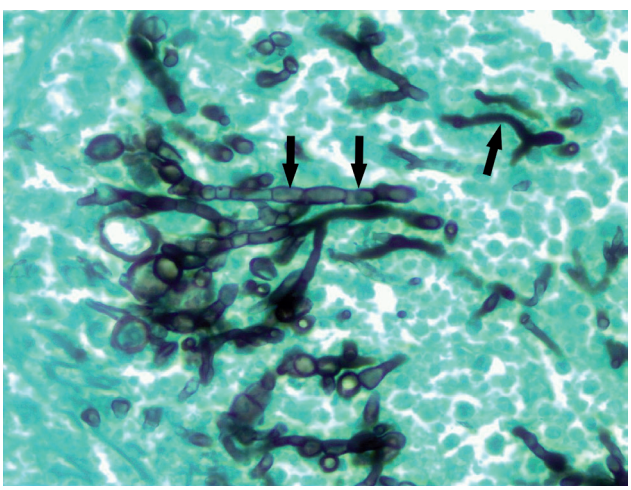

Figure 1 - Septated fungal hyphae (arrows) in the wall of the small bowel, branching at an acute angle (gmotics methenamine silver stain 400x).

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has become increasingly frequent among recipients of allogeneic hematopoietic-cell transplants, with an incidence rate of up to 12%.[2] Despite the availability of new azole and echinocandin antifungal drugs, the outcome remains poor, with a one-year mortality of 50-80%, making invasive aspergillosis one of the leading infection-related causes of death among recipients of allogeneic hematopoietic-cell transplants.[3] However, autopsy studies conducted in immunocompromised patients with disseminated IA have shown the GI tract to be a frequent site of sub-clinical involvement.[4] Our patient was immunocompromised with cutaneous evidence of aspergillosis, who developed systemic manifestations with GI involvement following further immunosuppression for presumed GVHD. Although aspergillosis of the GI tract appears to be rare in the immunocompromised host, it is important to have a high index of suspicion, since confusion with GVHD in post bone marrow transplant patients, as occurred in this case, can lead to additional immunosuppressive treatment, further compromising the patient.

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