Ante-mortem diagnosis of localized invasive esophageal aspergillosis in a patient with acute myeloid leukemia

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Abstract
Opportunistic infection with invasive aspergillosis (IA) is increasingly frequent in immunocompromised patients, particularly in those with hematological malignancies. In this setting, IA typically involves the lung, with extra-pulmonary involvement usually occurring in the setting of disseminated infection. We report a case of localized gastrointestinal IA complicating induction chemotherapy for acute myeloid leukemia (AML). Oral voriconazole was successful as primary treatment, with no evidence of progressive infection despite further myelosuppressive chemotherapy. A review of the literature suggests that although localized gastrointestinal IA is rare, involvement of the gastrointestinal tract is not uncommon in disseminated infection. Thus, in patients with hematological malignancies who develop significant gastrointestinal symptoms, we recommend that endoscopic investigations and biopsies are performed to exclude IA as a potential cause.

Keywords: Aspergillosis, acute myeloid leukemia, gastrointestinal infection, opportunistic, voriconazole

Introduction
Opportunistic infection with invasive aspergillosis (IA) is increasingly frequent in immunocompromised patients, particularly in those with hematological malignancies [1]. The lung is the most common organ involved, with extra-pulmonary involvement almost always occurring in the setting of disseminated infection [2–5]. Localized gastrointestinal IA is particularly uncommon, and is rarely diagnosed ante-mortem [3–7]. We report an ante-mortem diagnosis of localized gastrointestinal IA complicating induction chemotherapy for acute myeloid leukemia (AML). Oral voriconazole was successful as primary treatment, with no evidence of progressive infection despite further myelosuppressive chemotherapy.

Case report
A 71-year-old man presented with leukostasis syndrome complicating newly diagnosed AML (diploid cytogenetics; FAB classification AML M1; WHO classification AML without maturation). Peripheral blood counts at presentation were hemoglobin (Hb) 148 g/l, white cell count (WCC) 92.1 × 10^9/l (95% blasts, neutrophil count 0.25 × 10^9/l) and platelet count 19 × 10^9/l. Treatment was commenced with oral hydroxyurea (2 g tds) and daily leukapheresis, followed by induction chemotherapy comprising cytarabine 100 mg/m^2 intravenous (IV) days 1–5 and idarubicin 12 mg/m^2 IV days 4–5. Granulocyte colony-stimulating factor (G-CSF) was commenced from day 6. Doses were attenuated and the anthracycline delayed due to cardiac instability from leukostasis and renal impairment. Prophylactic oral fluconazole (200 mg d) and valaciclovir (500 mg d) were also commenced at day 1. These medications were continued until neutrophil recovery (> 1.0 × 10^9/l) at day 17. Despite achieving a complete hematological response on count recovery after initial chemotherapy, bone marrow examination performed on day 24 showed persistent residual leukemia (6% blasts). Re-induction chemotherapy was administered with 1 cycle of FLAG (fludarabine 30 mg/m^2 IV days 1–5, cytarabine 2 g/m^2 IV days 1–5 and daily G-CSF), achieving a complete morphological remission on repeat bone marrow aspirate and
trephine. The patient declined to proceed with consolidation chemotherapy and remains well 2 months post-completion of chemotherapy.

The initial induction chemotherapy was complicated by recurrent culture-negative febrile episodes during the neutropenic phase, treated empirically with IV cefepime, vancomycin and metronidazole until day 17, and subsequently with meropenem and vancomycin, which were ceased on day 21 following neutrophil recovery. On day 24, the patient experienced acute onset epigastric pain and bright red hematemesis. At the time, peripheral counts were Hb 115 g/l, platelets $459 \times 10^9$/l and WCC $9.6 \times 10^9$/l; coagulation profile was normal. Urgent gastroscopy showed an old blood clot present at the gastro-esophageal junction and an associated exophytic lesion in the distal esophagus (Figure 1). Biopsies of the lesion showed tissue necrosis, an associated acute inflammatory infiltrate and numerous fungal hyphae and yeast forms within the surface debris, morphologically consistent with invasive *Aspergillus* spp. (Figure 2). There was no evidence of systemic fungal infection on computed tomography scanning of the chest, abdomen and pelvis.

Oral voriconazole (400 mg bd loading dose, then 200 mg bd) was commenced as an outpatient and continued throughout the second cycle of chemotherapy. Oral omeprazole (20 mg bd) was also given. No further episodes of hematemesis or significant epigastric pain occurred. Repeat gastroscopy performed after hematological recovery from FLAG re-induction (and after a total of 39 days of voriconazole treatment) revealed a persistent small 0.5 cm diameter nodule at the distal esophagus, biopsies of which showed no evidence of residual fungal elements. Due to deranged liver function tests (alkaline phosphatase 372 IU/l (normal range 30–120 IU/l), gamma-glutamyl transferase 640 IU/l (normal range 7–32 IU/l), alanine transaminase 16 IU/l (normal range 0–50 IU/l) and bilirubin 11 µmol/l (normal range 0–17 µmol/l)) possibly attributable to voriconazole, oral itraconazole (100 mg bd) was substituted for voriconazole at this time, and continued for a further 7 weeks duration. No further gastroscopy was performed.

**Discussion**

IA is an increasingly common opportunistic infection in immunocompromised patients [1]. The most common predisposing disease for IA is hematological malignancy, due to disease- and/or therapy-related neutropenia, chemotherapy-induced defects in mucosal immunity and associated frequent corticosteroid use [1,4,5,8–12].

Our case is a rare example of localized gastrointestinal IA diagnosed ante-mortem. Three retrospective autopsy series demonstrate that while gastrointestinal tract involvement is not uncommon in the context of disseminated disease, it is rarely a localized site of infection [3–5]. Kami *et al.* [3] analysed 107 autopsies performed on patients with hematological malignancies and identified IA in 11% of cases. Although approximately one third of cases with disseminated infection had gastrointestinal tract involvement, including esophageal lesions in 5 cases, localized gastrointestinal infection was not observed. While some patients had previously described gastrointestinal symptoms, *Aspergillus* infection was neither clinically suspected nor diagnosed ante-mortem in any case. In a series of 3374 autopsies, including a large proportion of cardiac and oncology patients,

![Figure 1. Endoscopic appearance of an exophytic lesion in the distal esophagus.](image1.png)

![Figure 2. Esophageal biopsy, Periodic Acid Schiff stain (× 200). Fungal hyphae showing dichotomous branching consistent with *Aspergillus* spp.](image2.png)
Young et al. [5] observed aspergillosis in 98 cases, of which 21% involved the gastrointestinal tract. Again, in the majority of these (18 of 21), gastrointestinal infection occurred in the setting of disseminated disease. Finally, in a predominantly post-mortem series of 93 IA cases in patients with solid tumors and hematological malignancies reviewed by Meyer et al. [4], 9 patients (10%) were identified with gastrointestinal tract involvement, including 6 cases with esophageal ulcers. Although the majority of patients in this series with gastrointestinal IA were previously asymptomatic, it was not specified whether Aspergillus infection was suspected or diagnosed ante-mortem. Despite epigastric pain and hematemesis, the specific diagnosis of esophageal aspergillosis in our patient was not clinically suspected until after the gastrointestinal findings were known.

Although specimens for culture were not obtained in our case, the histological appearance of fungal hyphae with associated tissue damage is sufficient for definitive diagnosis of invasive fungal infection, in accordance with recently published guidelines [13].

Voriconazole, a broad-spectrum triazole, is a promising new agent for the treatment of invasive fungal infections. A recent randomized trial comparing voriconazole with conventional amphotericin B demonstrated a superior response rate (52.8% vs. 31.6%) and survival rate (70.8% vs. 57.9%) with use of voriconazole in this setting [14]. The main toxicities of voriconazole are transient visual disturbances and elevation of hepatic enzymes, as seen in our patient [14]. Although the optimal duration of anti-fungal therapy in IA is yet to be established, voriconazole treatment was continued for 12 weeks in the above trial [14]. Given the persistence of a small macroscopic nodule on repeat endoscopy in our patient, albeit with negative histology, we felt it appropriate to continue anti-fungal therapy for this duration with an alternative agent (itraconazole) after voriconazole was ceased.

In summary, we present a rare case of localized gastrointestinal IA complicating induction chemotherapy for AML. The infection was successfully treated with oral voriconazole, with no evidence of progressive infection following further chemotherapy. Although localized gastrointestinal IA is rarely reported, involvement of the gastrointestinal tract is not uncommon in disseminated IA. Thus, in patients with hematological malignancies who develop significant gastrointestinal symptoms, IA should always be considered as a potential differential diagnosis, and biopsies of any suspicious lesions seen at endoscopy taken for both histology and culture.

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References