

# Primary intestinal mold infection in children with solid tumors: a case report in an adolescent with Ewing sarcoma, and literature review

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## SUMMARY

We report a case of primary intestinal infection due to filamentous fungi in an adolescent with Ewing sarcoma. The clinical picture was that of peritonitis secondary to intestinal perforation and the diagnosis was established only on histopathological bases. This condition is very rare, and only one case of primary intestinal mold infection in children with solid tumors has been reported in the literature, although more records can be found describing similar conditions in other cancer patient populations (i.e. adults with solid tumors or children with hematological malignancies or patients receiving hemopoietic stem cell transplant).

Clinicians must be aware of this possibility since only an aggressive medical and surgical approach can improve patients' prognosis.

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## INTRODUCTION

Invasive fungal disease (IFD) due to filamentous fungi can represent a severe complication in children with acute leukemias or after hemopoietic stem cell transplant (HSCT), but is sporadic in solid tumors (Abbasi *et al.*, 1999; Castagnola *et al.*, 2006; Lehrnbecher *et al.*, 2010; Tragiannidis *et al.*, 2012; Castagnola *et al.*, 2014). Early diagnosis and treatment are the most important factors contributing to a positive outcome, but diagnosis can be difficult because of the nonspecific clinical symptoms and the low sensitivity and prolonged time required to obtain culture results. In addition, classic radiological findings are less frequent in pediatrics and although histopathology is the "golden standard" for deep organ localizations it might not be feasible due to the critical condition of these patients and failure to reach a specie-specific diagnosis (Oz *et al.*, 2011). The respiratory tract represents the most frequent localization of deep organ IFD (Castagnola *et al.*, 2006; Lehrnbecher *et al.*, 2010; Petrikos *et al.*, 2012; Castagnola *et al.*, 2014), while primary intestinal disease is very rare (Ismail *et al.* 1990; Prescott *et al.*, 1992; Mitchell *et al.*, 1996; Oliver *et al.*, 1996; Catalano *et al.* 1997; Abbasi *et al.*, 1999; Sousa *et al.*, 2002; Ouaiissi *et al.*, 2003; Pinto-Marques *et al.*,

2003; Mohite *et al.*, 2007; Castagnola *et al.*, 2009; Cheng *et al.*, 2009; Lehrnbecher *et al.*, 2010; Petrikos *et al.*, 2012; Tragiannidis *et al.*, 2012; Groll *et al.*, 2013). *Aspergillus* is the most frequently involved pathogen, but other etiologies have been described (Petrikos *et al.*, 2012; Groll *et al.*, 2014).

We describe a case of primary intestinal IFD due to filamentous fungi in a 16-year-old girl with Ewing sarcoma.

## CASE REPORT

The patient was diagnosed with Ewing sarcoma of the pubis in a center outside Italy, and received chemotherapy according to the EuroEwing99 protocol (vincristine, ifosfamide, doxorubicin and etoposide). After the end of this treatment surgical removal of the affected bone showed persistence of neoplastic tissue in approximately 20% of examined material and therefore further chemotherapy (vincristine, actinomycin-D, isosfamide) was needed. All treatment courses were administered without major infectious complications and a remission was obtained. One month after the end of chemotherapy the patient reported severe pain at the left lower limb. MRI suggested local relapse and therefore further cycles of chemotherapy and local radiotherapy were administered. This was followed by fever, neutropenia and worsening of her general clinical condition. At this time the patient was referred to our center on parental request. On admission she was febrile, but no longer granulocytopenic, with severe abdominal discomfort and empirical treatment with piperacillin-tazobactam and fluconazole was started. However, her clin-

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**Figure 1** - A) US scan image of the liver: hypo-anechoic nodule in the VII segment with irregular margins and slightly echogenic rim. B) Contrast-enhanced CT image of the liver: three hypodense nodules are shown in the VII, VIII and II segments.

ical condition worsened and she underwent emergency laparotomy. A large area of necrosis at the sigmoid colon with irregular transmural necrosis and perforation was detected. Histopathology revealed intestinal invasion by angioinvasive septated hyphae. Stool cultures resulted negative for filamentous fungi. Abdominal ultrasound and CT scan demonstrated hypo-anechoic irregular images in the liver parenchyma (Figure 1A-B), while the CT did not show any abnormalities or infiltrates. Plasma galactomannan antigen was negative as were cultures of peritoneal fluid and intestinal tissue samples. In the hypothesis of primary intestinal aspergillosis intravenous voriconazole was promptly started but despite intensive therapy the patient died.

## COMMENTS

Primary intestinal IFD due to filamentous fungi is a rare disease both in neutropenic and non-neutropenic cancer patients (Cohen *et al.*, 1992; Faber *et al.*, 1996; Catalano *et al.*, 1997; Abbasi *et al.*, 1999; Ouaïssi *et al.*, 2003; Pinto-Marques *et al.*, 2003; Trésallet *et al.*, 2004; Mohite *et al.*,

2007; Cheng *et al.*, 2009), whereas it can be more frequently observed as a secondary localization during disseminated infections (Abbasi *et al.*, 1999; Castagnola *et al.*, 2009; Petrikkos *et al.*, 2012; Tragiannidis *et al.*, 2012; Groll *et al.*, 2013). In children it has been mainly reported in neonates or after chemotherapy for acute leukemia or allogeneic HSCT (Petrikkos *et al.*, 2012; Tragiannidis *et al.*, 2012; Groll *et al.*, 2013), while it is an exceptional condition in solid tumors, with only one pediatric case reported in MEDLINE (Lehrnbecher *et al.*, 2006). Chemotherapy-induced severe mucositis can represent the portal of entry for this peculiar localization of IFD especially in the presence of neutropenia (van der Velden *et al.*, 2014). In our patient, we hypothesized an oral acquisition of the infection because of the clinical picture and absence of chest CT abnormalities. We could not confirm this hypothesis since we had no sample of food or medicines from her country of origin available for testing, but it is possible that a different local policy of using cooked foods and avoiding herbal medicine in cancer children, like the one we adopted in our center, could have saved the patient's life. In fact, colonization is a necessary condition for the development of IFD in the presence of immunosuppression, and intestinal colonization by filamentous fungi has been associated with ingestion of contaminated food (De Bock *et al.*, 1989; Thio *et al.*, 2000; Cheng *et al.*, 2009; Petrikkos *et al.*, 2012), spore-contaminated cornstarch used in the manufacturing of tablets or herbal and homeopathic remedies (Ismail *et al.*, 1990; Oliver *et al.*, 1996; Cheng *et al.*, 2009), or contaminated tongue depressors used for oropharyngeal examinations (Mitchell *et al.*, 1996; Cheng *et al.*, 2009). Different food habits, especially for foreign patients, and/or the use of "non conventional" medicines should be taken into account as a possible source of IFD, especially in the presence of unusual clinical pictures and pathogens.

Signs and symptoms of primary intestinal IFD are non-specific, and in the majority of cases the diagnosis is made by histology of the removed gut. In our case, no fungi grew from peritoneal fluid or intestinal tissue samples and plasma galactomannan antigen was also negative, while it was not performed on the peritoneal fluid. For an indirect, presumptive diagnosis of IFD detection of plasma galactomannan antigen has been shown useful for aspergillosis also in neutropenic children (Castagnola *et al.*, 2010), but not in the absence of neutropenia (Groll *et al.*, 2014), and there is no proof of its reliability in peritoneal fluid. At present no indirect test is available for diagnosis of zygomycosis. Therefore, even if histology could have been suggestive of aspergillosis, in our patient a definitive diagnosis could not be made and we could not completely exclude a diagnosis of zygomycosis. Treatment of primary intestinal IFD due to filamentous fungi is frequently disappointing, with high mortality rates (De Bock *et al.*, 1989; Ismail *et al.*, 1990; Cohen *et al.*, 1992; Prescott *et al.*, 1992; Mitchell *et al.*, 1996; Oliver *et al.*, 1996; Catalano *et al.*, 1997; Sousa *et al.*, 2002; Ouaïssi *et al.*, 2003; Pinto-Marques *et al.*, 2003; Trésallet *et al.*, 2004; Lehrnbecher *et al.*, 2006; Mohite *et al.*, 2007; Saitoh *et al.*, 2007; Cheng *et al.*, 2009; Petrikkos *et al.*, 2012; Traggiannidis *et al.*, 2012; Groll *et al.*, 2013). The best strategy is probably represented by the combination of surgery associated with high-dose liposomal amphotericin B or posaconazole in the case of zygomycetes (Cornely *et al.*, 2014), or voriconazole in patients with infection due to *Aspergillus* or other filamentous fungi like *Scedosporium* or *Fusarium* (Groll *et al.*,

2014). This different susceptibility to antifungal drugs further underlines the need for a complete etiological diagnosis in order to use the most appropriate drug and dosages and strategy of initial treatment in case of suspected IFD pending pathogen identification. Indeed, nowadays in our center liposomal amphotericin B represents the first line therapy of suspected mold IFD, until a clear etiological diagnosis or at least a highly probable identification has been achieved. This approach together with diagnostic aggressiveness can really improve survival in children with cancer and IFD (Castagnola *et al.*, 2014).

### Conflict of interest to declare

None.

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