

Gastrointestinal basidiobolomycosis in a patient suffering from duodenal ulcer with perforation: First case report from Italy

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SUMMARY

Gastrointestinal basidiobolomycosis (GIB), an unusual fungal infection caused by the fungus *Basidiobolus ranarum*, is rarely reported in the medical literature. GIB is difficult to diagnose because its clinical presentation is non-specific and has no identifiable risk factors. We report here the first case of GIB diagnosed in Italy in a patient suffering from a duodenal ulcer with perforation. The patient was successfully treated with itraconazole. The absence of non-specific signs and symptoms of GIB may delay a definitive diagnosis and treatment. A microbiological investigation should always be requested in order to reach a rapid and definitive diagnosis and to rule out other intestinal diseases.

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INTRODUCTION

Gastrointestinal basidiobolomycosis (GIB) is a rare condition caused by the fungus *Basidiobolus ranarum*, belonging to the order of Entomophthorales, class Zygomycetes. It is an environmental saprophyte that is widespread globally but mainly presents in tropical regions (Africa, South America and Asia), where the greatest number of cases of basidiobolomycosis are found. Typically, this fungus causes chronic subcutaneous infection mainly in children as young as one month of age (Mendiratta *et al.*, 2012). If not treated, this infection could be similar to soft tissue tumors and in some case have been reported as huge subcutaneous infections causing perineal intestinal obstruction or intraperitoneal spread (Ramesh *et al.*, 2010; Singh *et al.*, 2008). It seems that this fungus infection is acquired by exposure to *B. ranarum* after minor trauma to the skin or by insect bites. *B. ranarum* also causes gastrointestinal infection that may cause inflammatory obstruction. Deep visceral varieties of entomophthoramycosis caused by *B. ranarum* can involve the gastrointestinal tract with spread to adjacent areas (Shaikh *et al.*, 2016). Clinical signs and symptoms of GIB mimic those of inflammatory bowel disease (Gugnani *et al.*, 1999). In fact, GIB is misdiagnosed as other intestinal infections (tuberculosis, amebiasis), malignancy or Chron's disease (Almoosa *et al.*, 2017; Khan *et al.* 1998). As GIB is a rare condition, its clinical characteristics are poorly understood. Although it is unclear how

the fungus is introduced into the host's gastrointestinal tract, it has been hypothesized that this occurs through ingestion of soil, animal feces, or food contaminated by either. Ingestion and rectal inoculation seem to be the most likely routes of infection (Bittencourt *et al.*, 1991; Pasha *et al.*, 1997; Schmidt *et al.*, 1986; Edington *et al.*, 1964; Carvalho *et al.*, 1997; Smilack *et al.*, 1998; Zavasky *et al.*, 1999; De Aguiar *et al.*, 1980; Khan *et al.* 2001). Since the first case of GIB reported in 1964, only 122 cases have been reported worldwide (1 from Brazil, 1 from the Netherlands, 1 from Oman, 1 from Qatar, 1 from Thailand, 2 from France, 2 from Kuwait, 6 from Iraq, 21 from the US, 24 from Iran, and 62 from Saudi Arabia) (Mohammadi *et al.*, 2018). Table 1 provides the main characteristics of the GIB cases reported by Mortada *et al.*, 2011; Vikram *et al.*, 2012; Geramizadeh *et al.*, 2015; Lyon *et al.*, 2001; Zavasky *et al.*, 1999; Geramizadeh *et al.*, 2012; Mohammadi *et al.*, 2018. GIB is extremely rare and extremely difficult in terms of diagnostics (Gugnani *et al.*, 1999). We describe

Table 1 - Main characteristics of the 122 GIB cases reported in the literature from 1964 to 2018.

Characteristics	No. Patients (Proportion %)
Symptoms	
Abdominal pain	110 (90%)
Abdominal mass	49 (40%)
Laboratory tests	
Culture total	82 (67%)
Positive culture	47 (57%)
Histopathology total	116 (95%)
Positive Histopathology	115 (99%)
Therapy and outcome	
Azole	110 (90%)
Death	20 (16%)

Key words:

Fungal infection; Basidiobolomycosis; Duodenal ulcer; *Basidiobolus ranarum*.

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below the first case of GIB diagnosed in Italy in an immunocompetent man suffering from a duodenal ulcer with perforation.

CASE REPORT

A 78-year-old Caucasian Italian man presented to the Accident and Emergency department of our hospital for abdominal pain, vomiting and loss of appetite. Medical history revealed a 30-year history of abdominal pain episodes caused by a gastric ulcer treated with antacids (aluminum hydroxide plus magnesium hydroxide and rabeprazole sodium) and prostatic hypertrophy treated with finasteride. Initial laboratory tests were normal (blood count, prothrombin activity, serum electrolytes, serum creatinine, biochemical liver and pancreas function tests) except for elevated serum procalcitonin (PCT) levels (4.72 ng/ml). After surgery, laboratory tests were still normal and PCT levels decreased at 48 h (1.60 ng/ml) and 72 h (0.93 ng/ml). An abdominal x-ray obtained with the patient in a supine position revealed evidence of a pneumoperitoneum with gas under the subdiaphragmatic region. The findings were suggestive of a duodenal ulcer with perforation. The patient was handed over to the surgical team, who administered ceftriaxone (2 gr.

i.v.) and paracetamol (1000 mg i.v.) therapy. The diagnosis of peritonitis was based on laparoscopic findings of purulent fluid in the peritoneal cavity, and a sample of peritoneal fluid was sent to the microbiology laboratory in two BacT/ALERT blood culture bottles for aerobic and anaerobic germs (bioMérieux, Marcy-l'Étoile, France). The blood culture bottles were incubated in a BacT/ALERT VIRTUO (bioMérieux, Marcy-l'Étoile, France) detection system. The aerobic bottle, which positivized after 34 hours, was cultured on blood agar (B), chocolate agar (C), MacConkey agar (M) and Sabouraud's dextrose agar (S). The B, C, and M culture media were incubated at 37°C and the S at 30°C. The colonies grew rapidly on B, C and S agar, attaining a diameter of 2-3 mm within 18 hours; their color was greyish and opaque, rugose with a waxy texture (Figure 1). No growth was observed on M agar. As the growth progressed, the formation of many satellite colonies was observed due to forced ejection of sporangioles (ballistospores). Slide cultures revealed a large number of asexual spores (sporangiospores), some of which had a knob-like adhesive tip (Figure 2). Based on these microscopic and macroscopic findings, a zygomycete belonging to the order of Entomophthorales (probably *Basidiobolus* spp.) was identified as the causative agent. The identity of the isolate was then confirmed by DNA sequencing. DNA amplification and sequencing of the ITS region (internal transcribed spacer) was carried out by the Institute of Microbiology at the Catholic University of the Sacred Heart in Rome. The fungus-specific universal primers ITS1 (5'-TCCGTAGGTGAACCTGCGG-3') and ITS4 (5'-GCATATCAATAAGCGGAGGA-3') were used to amplify the ITS region (Leaw *et al.*, 2006). Amplification was performed using the Hotstart Taq Master Mix Kit (Qiagen, Hilden, Germany). The amplified DNA was sequenced using the ABI PRISM 3130xl Genetic Analyzer (Applied Biosystems, Foster City, California, USA) tool. The sequences were compared to reference data available at the GenBank database using BLAST (<http://www.ncbi.nlm.nih.gov/BLAST/>). Post-operatively, the patient did well and was successfully treated by targeted therapy with itraconazole (200 mg administered twice per day).



Figure 1 - Colonies grown on blood agar after 18 hours at 37°C (2-3 mm diameter).



Figure 2 - Sporangiospores; the red arrow shows the presence of a knob-like adhesive tip. (Slide culture, 400x).

DISCUSSION

The presumptive identification of a zygomycete belonging to the Entomophthorales order was performed by microscopy examination just three days after the sample had been received by the microbiology laboratory. The identification of *B. ranarum* by DNA sequencing led to the definitive diagnosis of GIB in a patient who had never traveled out of Italy. In most cases described in the literature, patients had leukocytosis and eosinophilia (Vikram *et al.*, 2012; Geramizadeh *et al.*, 2012; Geramizadeh *et al.*, 2015; Mohammadi *et al.*, 2018). In our case report, the patient's laboratory tests were normal, except for PCT. Although PCT is not a specific indicator of fungal infections, it can be induced in persistent and invasive fungemia (Gérard *et al.*, 1995; Ortega *et al.*, 2004; Distefano *et al.*, 2004). Charles *et al.* (2006) found a significantly lower PCT level in patients with candidemia (median 0.65 ng/ml) compared to those with bacteremia (median 9.75 ng/ml). A PCT level higher than 5.5 ng/ml demonstrated a 100% negative predictive value and 65% positive predictive value for sepsis caused by *Candida* spp. In cases

where PCT is 1-5 ng/ml in conjunction with a fungal infection, its decrease could be related to the success of the therapy (Jemli *et al.*, 2007). In our case, the decrease in PCT levels followed the surgery, as the targeted therapy with itraconazole was started three days after the surgical treatment. However, other cases of patients with severe fungal infections report low or non-existent levels of PCT (Huber *et al.*, 1997; Beaune *et al.*, 1998). The patient described in this case report had 30-year history of abdominal pain episodes and a gastric ulcer treated with antacid. Abdominal pain, the most common presenting symptom of GIB, could be related to the presence of *B. ranarum*, as reported in the literature (Flicek *et al.*, 2014). Potential risk factor of GIB include prior medical treatment for peptic ulcer disease with antacid (16% of patients had peptic ulcer disease or gastritis) (Vikram *et al.*, 2012). Antacids may contribute to the pathogenesis of GIB by decreasing stomach acidity and allowing the organism to survive the gastric passage, which has been identified as a risk factor for bacterial gastroenteritis (Marshall Lyon *et al.*, 2001; Littman *et al.*, 1990; Neal *et al.*, 1994; Neal *et al.*, 1996). The source of infection in our case was not identified. *B. ranarum* is a ubiquitous soil fungus commonly found in decaying plants. It may also be present as a commensal in the intestinal tract of amphibian frogs and toads, fish, and reptiles (Okafor *et al.*, 1984). The patient had no unusual exposure to soil and denied contact with any animal species in which the organism is known to be a saprophytic colonizer. The mode of acquisition of the disease remains poorly understood. To confirm a case of GIB, the key element is either the characteristic histopathological appearance of the biopsy (tissue biopsy shows eosinophilic infiltration and typical Splendore-Hoeppli phenomenon) or isolation of *B. ranarum* from specimens (Vikram *et al.*, 2012). In our case report, GIB was diagnosed only by isolation of *B. ranarum* from the patient's peritoneal fluid samples (no histopathological exams were carried out). Bigliuzzi *et al.* (2004) reported the first case of disseminated basidiobolomycosis infection in Italy. In this case, cultures and serologic tests for *B. ranarum* or other Entomophthorales agents had not been carried out because of clinical suspicion of neoplasm or vasculitis. The diagnosis was made on the basis of autopsy findings. The gold standard for definite diagnosis of GIB is microbial culture of *B. ranarum* from fresh aspiration or surgical specimens (Zabolinejad *et al.*, 2014; Al-Maani *et al.*, 2014) and requires a high level of clinical suspicion by the clinician and the mycologist. *B. ranarum* does not survive at 4°C. Sabouraud agar is an adequate medium, and visible growth is usually present 2-3 days after incubation at 25-30°C (Kwon-Chung *et al.*, 1992). Because of the nonspecific signs and symptoms presenting, GIB can cause intestinal perforation and may masquerade as another clinical entity, delaying definitive diagnosis and treatment. If untreated, the mortality rate of disseminated disease approaches 16%. In order to consider GIB in the differential diagnosis, we suggest microbiological investigation in cases of abdominal pain with a mass (Mortada *et al.*, 2011), and a clinical profile suggestive of malignancy (Nemenqani *et al.*, 2009).

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