Case Report

A case of pediatric gastrointestinal basidiobolomycosis mimicking Crohn's disease

A review of pediatric literature

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ABSTRACT

يعد مرض البسيديوبولوميكوسيس مرض فطري نادر نتيجة الإصابة بفطر يدعى باسيديو راناروم. الغالبية العظمى من الحالات المنشورة لمرض البسيديوبولوميكوسيس والتي أصابت الجهاز الهضمي أتت من مناطق استوائية وتحت استوائية. هنا نحن ننشر حالة لطفل سعودي مصاب بمرض البسيديوبولوميكوسيس في الأمعاء الدقيقة أظهر في البداية علامات أكلينكية مشابه لالتهاب الزائدة الدودية قبل أن يشخص عن طريق الخطأ بمرض التهاب الامعاء « كرونز ». حالتنا هذه تعتبر الأولى لأثبات علاج هذا المرض في الأطفال بالاستعمال المنفرد لعقار فوريكونازول، المضاد للفطريات. بالإضافة لذلك، نقوم بمراجعة الموسوعة الطبية المنشورة عن حالات البسيديوبولوميكوسيس والتي أصابت الجهاز الهضمي لدى الأطفال.

Basidiobolomycosis is a rare fungal infection caused by basidiobolus ranarum. The vast majority of gastrointestinal basidiobolomycosis cases were reported from tropical and subtropical regions. We report a Saudi pediatric patient with ileal basidiobolomycosis and initial clinical presentation mimicking acute appendicitis before being misdiagnosed as Crohn's disease. Our case is the first to report effective treatment of pediatric gastrointestinal basidiobolomycosis using voriconazole mono-therapy. In addition, we present extensive review of pediatric gastrointestinal basidiobolomycosis in medical literature.

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Basidiobolomycosis is a rare fungal infection caused by Basidiobolus ranarum. Basidiobolus ranarum is an environmental saprophytic fungus found worldwide in soil, decaying organic matter, and gastrointestinal tracts of some animal. Because gastrointestinal basidiobolomycosis is a rare disease with non-specific gastrointestinal manifestations, its clinical presentation can be readily confused with commoner gastrointestinal diseases such as infectious, inflammatory, and infiltrative diseases of the bowel. We report a Saudi pediatric patient with basidiobolomycosis with initial clinical presentation mimicking acute appendicitis before being misdiagnosed as ileal Crohn's disease. In addition, we present extensive review of pediatric gastrointestinal basidiobolomycosis in medical literature with the aim to increase awareness for this fungal infection and its diagnostic challenge. Increased awareness of this clinical entity will lead to earlier diagnosis and good prognosis.

Case Report. A 4-year-old Saudi boy presented to a local hospital in the South West of Saudi Arabia with high-grade fever and right lower abdominal pain for 4 months and vomiting for 5 days. These symptoms were associated with weight loss but no diarrhea. Laparotomy was performed for suspected appendicitis. Intraoperatively, the appendix was inflamed, with thickening of the wall of terminal ileum, cecum, and ascending colon with multiple enlarged lymph nodes. The resected appendix was reported to be inflamed and biopsies from the mesenteric lymph nodes showed follicular hyperplasia. Three weeks later, the child was still symptomatic and referred to our hospital with a suspected diagnosis of ileal Crohn's disease.

Evaluation in our hospital, revealed a pale undernourished young child with a high grade fever. On abdominal examination, there was tenderness and guarding over the right lower quadrant without identified mass or hepatosplenomegaly. Other systemic examination was unremarkable. Initial laboratory

investigations showed hemoglobin 9.6 gm/dl, WBC 17,000 x10^6/l, eosinophils % 13.6, platelets 777x10^9/l (normal, 150-450 x10^9/l), erythrocyte sedimentation rate (ESR) 93 mm/hr (normal, 0-20 mm/hr), albumin 30 g/L (normal, 35-50 gm/l), and normal liver function tests. Further investigations showed high anti-*Saccharomyces cerevisiae* antibodies (ASCA) IgG 35.6 units (normal, 0-20 units), antibodies to the *Escherichia coli* outer membrane protein C (OmpC) 38.4 units (normal, 0-20 units), negative peri-nucleolar anti-neutrophil cytoplasmic antibodies, negative HIV serology, normal celiac profile, normal serum immunoglobulins, negative tuberculin test, negative serum Quantiferon-TB, and negative salmonella, brucella, and yersinia titers.

Abdominal CT scan showed marked mural thickening involving the terminal ileum (**Figure 1**), cecum and proximal ascending colon, mild narrowing in distal ileum and dilatation of the bowel pre-stenosis, and multiple enlarged mesenteric lymph nodes. Further diagnostic evaluation included normal upper endoscopy and colonoscopy that revealed an ulcerative, necrotic, and erythematous mucosa of the terminal ileum with stricture 5-6 cm from ileocecal valve (**Figure 2**).

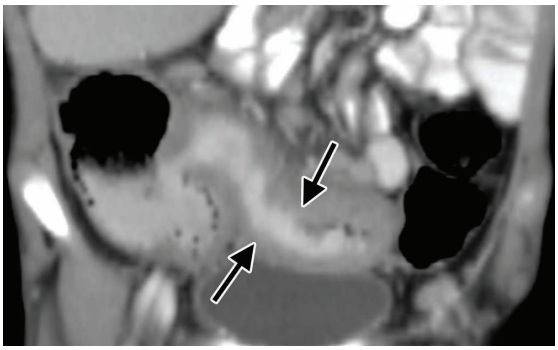

Figure 1 - A computerized tomography scan of the abdomen showing wall thickening of terminal ileum (arrow).

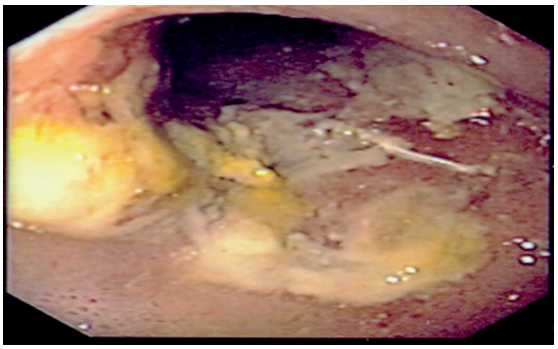

Figure 2 - Endoscopic view of ulcerative, erythematous lesion in terminal ileum.

Histopathology of biopsies from terminal ileum showed ulcerative mucosa extensively infiltrated by eosinophils, lymphoid hyperplasia, no granuloma formation, no abnormal malignant cells or dysplastic changes, negative fungal staining and negative Zeil-Nelson satin for acid fact bacilli. Polymerase chain reaction for mycobacterium tuberculosis DNA in ileal biopsies was negative. Biopsies from esophagus, stomach, duodenum, and colon were normal. The ileal involvement and positive anti-Saccharomyces cerevisiae antibodies (ASCA) and *Escherichia coli* outer membrane protein C (OmpC) serology led to consideration of Crohn's disease as a diagnostic possibility, but therapeutic trial with steroids was postponed awaiting results of work up for infectious diseases.

Initial management of the child included nutritional support via peripheral parenteral nutrition, and intravenous metronidazole, vancomycin, and ceftazidim. As the fever persisted and histopathology result was not conclusive, the patient underwent laparotomy to obtain adequate tissue biopsies for evaluation. Intraoperatively, the distal small bowel was found to be inflamed, thickened, and matted together with adhesions and the omentum was inflamed and encroaching on terminal ileum. Biopsies obtained from the omentum and lymph nodes revealed necrotizing granulomatous inflammation with extensive eosinophil infiltrate, Splendore-Hoeppli phenomenon (**Figure 3**), and broad septated fungal hyphae (**Figure 4**) consistent with basidiobolus fungus. Culture of intraoperative specimen grew basidiobolus ranarum. The patient was started on voriconazole 100 mg IV twice a day, which was followed by defeverescence and resolution of abdominal

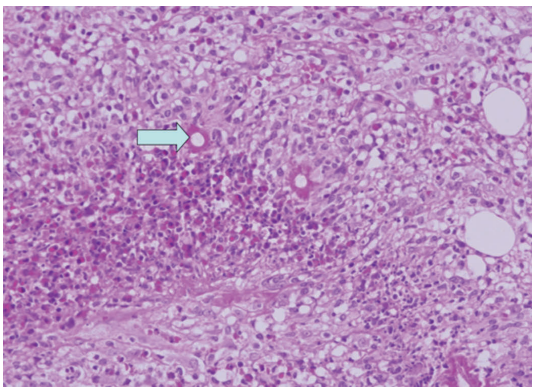

Figure 3 - Histopathological examination of intraoperatively obtained specimen from the abdominal mass shows extensive eosinophilic infiltrate and the Splendore-Hoeppli phenomenon (arrow). [Eosin and hematoxylin stain; Magnification X 40].

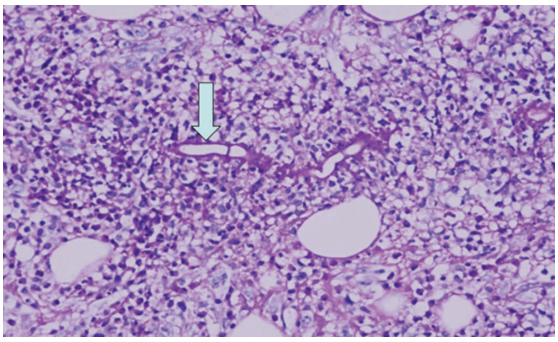

Figure 4 - Periodic acid Schiff staining of biopsy from the abdominal mass shows broad, septated fungal hyphae (arrow) [magnification X 40].

pain in one week. Voriconazole was continued for one year. On follow up in clinic, the child continued to do well with good appetite and good weight gain.

Discussion. Gastrointestinal basidiobolomycosis is an indolent fungal infection that occurs primarily in specific geographic regions in the world such as Southwestern province (Tohama region) of Saudi Arabia,[1-7] Arizona State in United States,[8] Brazil,[9,10] Iran,[11,12,14] and Nigeria.[13] The warm and humid climate, that characterizes these regions, might enhance the growth of the fungus. Ingestion of soil, animal feces, and foods contaminated by fungus are the most likely routes of infection. To the best of our knowledge 28 pediatric cases of gastrointestinal basidiobolomycosis have been reported so far in the English literature. Review of the literature (**Table 1**) revealed that majority of the cases have been reported from Saudi Arabia (n=14; 50%) and Iran (n=11; 39%); age range 13 months to 16 years (median 8 years), and 25 were males. Although the first pediatric case was reported in 1964,[13] 25 of the 28 cases have been reported over the past decade, which might reflect escalating epidemiology of this fungal infection or an increased awareness of this entity, or both. All patients presented with fever, abdominal pain, and high peripheral blood eosinophilia. Other symptoms varied according to the site of involvement and included jaundice, vomiting, diarrhea, and hematochezia. A mass involving part of the gastrointestinal tract was observed in all patients as visualized on imaging study or intraoperatively. Colon was the most commonly involved site (n=20; 71.5%), followed by hepatobiliary system (n=13; 46.5%), ileum and mesentery (n=4; 14%), stomach (n=3; 11%), rectum and urinary system (n=2; 7%), duodenum and pancreas (one patient each). In the majority, nonspecific and indolent signs and symptoms led to an initial consideration of abdominal malignancy,[5,14] inflammatory bowel disease,[7] intestinal tuberculosis,[1,7] appendicitis and appendicular mass,[1,2,5] schistosomiasis,[4] and amebiasis.[12] Fistulization, perforation, and abscess formation, may be present and masquerade as Crohn's disease.[7] Indeed, the ileal disease and positive ASCA and OmpC antibodies in our case caused diagnostic confusion and consideration of Crohn's disease.

On histopathological examination, basidiobolus ranarum seems to involve the non-mucosal layer of the gastrointestinal tract, therefore small superficial endoscopic biopsy specimens like in our case usually show non-specific inflammation and might fail to detect the fungus, which usually causes granulomatous inflammation that extends into submucosa, subserosa, and adipose tissue. Surgical excision of the mass involving the intra-abdominal organ was undertaken in 14 patients (73.6%) which facilitated the definitive culture-proven diagnosis. Seven out of 28 cases died (25%); disseminated intra-abdominal disease and late diagnosis was the cause in 4 cases,[1,14] and unavailability of effective anti-fungal agents, more than 3 decades ago, was the cause in 3 cases.[9,10,13] Based on the limited information available from a review of the literature, it appears that surgical resection of the infected tissue and prolonged treatment with one of the newer azoles offer the best available therapeutic options. It is unclear whether anti-fungal alone is sufficient or if simultaneous resection of the affected tissue is necessary to eradicate the infection. Result of mono-therapy with amphotericin B was unsatisfactory as 50% of basidiobolus ranarum isolates were resistant to amphotericin B.[15] Itraconazole mono-therapy, in addition to surgical resection of the intra-abdominal mass, have been proven to be effective to cure the infection. Voriconazole, a derivative of fluconazole, has potent activity against a broad spectrum of clinically significant pathogens, including Aspergillus, Candida, Cryptococcus, Fusarium, and Scedosporium.[16] A dosage of 7 mg/kg every 12 hours is recommended in pediatric age group.[17] Oral bio-availability of voriconazole has been claimed to be close to 100% so that no dose adjustment is necessary when switching from intravenous to oral administration.[18] Voriconazole has been safe and well tolerated; however, its use is also associated with a number of concerns. There is the possibility of serious adverse events, such as prolonged visual disturbances, QT-interval prolongation and hepatic toxicity; therefore, close monitoring of cardiac, visual, and liver function is strongly recommended.[17] Recently, it has been effectively used in combination with amphotericin B

Table 1 - Summary of the medical literature for pediatric gastrointestinal basidiobolomycosis.

Case	Age / Gender	Country/ Reference	Clinical presentation	Affected organ	Surgical procedures	Treatment	Outcome
1	12 yr/M	Saudi[1]	Abdominal pain, fever, abdominal distension. The child was treated	Ascending colon, liver	Right hemicolectomy, biliary duct stenting	Ampho-B Itraconazole	Cured
2	12 yr/M	Saudi[1]	Abdominal pain, fever	Liver, right kidney	Resection of terminal ileum, cecum and ascending colon	Ampho-B Itraconazole	Cured
3	12 yr/M	Saudi[1]	Abdominal pain, fever, appendicular mass,	Ascending colon, liver	Right hemicolectomy	Ampho-B Itraconazole	Cured
4	4 yr/M	Saudi[1]	fever, abdominal pain	Liver	FNA from liver lesion	Ampho-B Itraconazole	Cured
5	3 yr/M	Saudi[1]	Abdominal pain, fever, abdominal distension, weight loss.	Disseminated involving liver, spleen, gallbladder, and mesentery	FNA from liver lesion	Ampho-B 5-flucytosine Ambisome	Died
6	7 yr/M	Saudi[1]	Abdominal pain, fever, jaundice, weight loss. Hepatosplenomegaly, gastrointestinal bleeding	Liver, duodeno-biliary fistula	On laparotomy extensive highly vascular inoperable lesions	Ampho-B	Died
7	12 yr/M	Saudi[2]	Abdominal pain, fever, vomiting, hematochezia	Right colon, liver	Right hemicolectomy	Itraconazole	Cured
8	1.5 yr/M	Iran[11]	Abdominal pain, fever, diarrhea, hematochezia, bowel obstruction	Rectum, urinary bladder	Laparotomy: mass resected, proximal colostomy	Ampho-B	Died
9	4 yr/M	Brazil[9]	Abdominal pain, fever, diarrhea, epigastric mass	Stomach, transverse colon	Surgery	Surgery	Died
10	13 yr/M	Brazil[10]	Abdominal pain, fever, anorexia, memory loss	Stomach, duodenum, transverse colon, pancreas, liver, biliary system, intestinal obstruction	No surgery	No therapy	Died
11	6 yr/M	Nigeria[13]	Skin infection, rectal obstruction	Ileum, transverse colon, rectum, bladder	No surgery	Antibiotics, Iodide therapy	Died
12	2.5 yr/M	Saudi[7]	Fever, abdominal pain, vomiting, diarrhea, weight loss. Mass in the right iliac fossa.	Ileum, ascending colon, mesenteric lymph nodes	Laparotomy: Material from the retroperitoneal mass obtain.	Ampho-B voriconazole	Cured
13	10 yr/M	Saudi[4]	Fever, abdominal pain, vomiting, abdominal tenderness, rigidity.	Large cecal mass	Cecal perforation was found and mass excised	Itraconazole	Cured
14	13 yr/M	Saudi[3]	Acute abdominal pain, diffuse abdominal, rigidity and tenderness	Ascending colon	Right hemicolectomy	Itraconazole	Cured
15	12 yr/M	Iran[12]	Abdominal pain, bloody diarrhea, fever, vomiting	Descending colon	Left hemicolectomy	Ampho B Posoconazole	Cured
16	6 yr/M	Saudi[5]	Abdominal pain, fever	Cecum, liver	Incisional biopsy from cecal mass	Ampho-B Itraconazole	Cured
17	13 yr/F	Saudi[5]	Abdominal pain, fever	Ascending colon	Right hemicolectomy	Ampho-B Itraconazole	Cured
18	8 yr/F	Saudi[5]	Fever, abdominal distension, weight loss, jaundice	Mass at porta-hepatis causing biliary obstruction and dilated pelvis of kidney	Non-rescetable mass obstructing bile duct. Hepaticojejunostomy	Ampho-B Itraconazole	Cured
19	4 yr/M	Saudi[6]	Fever, right upper quadrant pain	Liver	Left hepatectomy	Ampho-B Itraconazole	Cured
20	15 mo/F	Iran[14]	Abdominal pain and distension	Stomach, colon, mesentery	Resection of involved segment	Ampho-B Itraconazole	Died
21	5 yr/M	Iran[14]	Abdominal pain	Colon	Resection of involved segment	Ampho-B Itraconazole	Cured
22	5 yr/M	Iran[14]	Abdominal pain	Colon	Resection of involved segment	Ampho-B Itraconazole	Cured
23	2 yr/M	Iran[14]	Abdominal pain and diarrhea	Terminal ileum, colon	Resection of involved segment	Ampho-B Itraconazole	Cured
24	16 yr/M	Iran[14]	Abdominal pain	Colon	Resection of involved segment	Ampho-B Itraconazole	Cured
25	16 mo/M	Iran[14]	Abdominal pain and diarrhea	Stomach, small intestine, colon, mesentery	Resection of involved segment	Ampho-B Itraconazole	Died
26	13 mo/ M	Iran[14]	Abdominal pain, bloody stool	Colon	Resection of involved segment	Ampho-B Itraconazole	Cured
27	2.5 yr/M	Iean[14]	Abdominal pain and constipation	Colon	Resection of involved segment	Ampho-B Itraconazole	Cured
28	2 yr/M	Iran[14]	Abdominal pain and distension	Colon	Resection of involved segment	Ampho-B Itraconazole	Cured
Present case	4 yr/M	Saudi	Fever, abdominal pain	Ileum	Incisional biopsies from mass at terminal ileum	Voriconazole	Cured

Ampho-B - amphotericin-B, F - female, FNA - fine needle aspiration, M - male, mo - month, yr - year, FNA - fine needle aspiration

to treat pediatric gastrointestinal basidiobolomycosis.[7] Our case is the first to report effective treatment of pediatric gastrointestinal basidiobolomycosis using voriconazole mono-therapy.

In conclusion, gastrointestinal basidiobolomycosis leads to diagnostic confusion, and is associated with increased morbidity and mortality. It should be kept in the differential diagnosis of inflammatory diseases of the gastrointestinal tract, especially in patients from Tohama region of Saudi Arabia and presenting with persistent eosinophilia.

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