Endoscopic diagnosis of intestinal penicilliosis marneffei: report of three cases and review of the literature

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Diarrhea is the most common GI presentation of immunocompromised patients, especially those with acquired immunodeficiency syndrome (AIDS).[1,2] More than 50% of patients with AIDS have diarrhea caused by a variety of pathogens during their illness.[1,2] Intestinal mycoses are uncommon in immunocompromised patients, however, and may be caused by *Cryptococcus neoformans*[3] and *Histoplasma capsulatum*.[4]

Penicillium marneffei, an emerging facultative intracellular pathogen and the only thermally dimorphic fungus of the genus *Penicillium*, can cause disseminated infection in patients residing in or traveling to areas where the organism is endemic, which include southeast Asia, southern China, and Hong Kong.[5-17] With the human immunodeficiency virus (HIV) pandemic, the number of cases of penicilliosis marneffei has increased markedly during the past 5 years, from 30 cases during the period between 1973 and 1990 to more than 160 by the end of 1995.[16] After extrapulmonary tuberculosis and cryptococcosis, penicilliosis marneffei ranks as the third most common opportunistic infection in HIV-infected patients in Thailand.[14] Although *P marneffei* has become an increasingly important cause of invasive mycoses in immunocompromised hosts, it has been rarely implicated as a cause of intestinal mycoses. As of December 1997, only four cases of intestinal penicilliosis marneffei have been reported in English language publications and only one was diagnosed antemortem by endoscopy.[8,9,12,17] Here we report three cases in which immunocompromised patients, two with AIDS and one after renal transplantation, presented with intestinal penicilliosis marneffei where early diagnosis was made possible by endoscopy.

CASE REPORT

Case 1

A 33-year-old man, who had undergone renal transplantation in 1991 and again in 1994, was admitted because of worsening renal function and passage of tarry stool. He had been otherwise well except for ureteral tuberculosis 3 years earlier for which he was treated with a 12-month course of antituberculous therapy. He gave no history of travel outside of Taiwan and had been treated with prednisolone, azathioprine and cyclosporine. Ten months earlier cyclosporine was replaced with FK-506 (tacrolimus) because of gradually worsening renal function. Serum creatinine was in the range of 8.3 to 9.6 mg/dL (normal value 0.6-1.2).

He developed cough, purulent sputum, and rhinorrhea without fever during the 2 weeks prior to admission. Physical examination was unremarkable. Chest radiography was reportedly negative. Cefaclor was given without benefit. In addition to passage of tarry stool, he had developed a tongue ulcer.

At admission, he appeared pale and looked chronically ill with mild respiratory distress. Temperature was 35.8°C, pulse rate 100/min, respiratory rate 28/min, and blood pressure 110/80 mm Hg. Oral candidiasis was found in addition to an indurated tongue ulcer of 0.8 × 0.8 cm. Hemoglobin was 4.9 gm/dL, white blood cell count 1.350 k/mm^3, and platelet 10 k/mm^3. Both serum albumin (normal values in parentheses, 3.5-5.0) and globulin (2.3-3.5) were 2.6 gm/dL, blood urea nitrogen 207 mg/dL (4.5-24), creatinine 9.6 mg/dL (0.6-1.2), alkaline phosphatase 483 U/L (69-238), calcium 2.1 mmol/L (2.02-2.60), phosphate 6.6 mmol/L (2.7-4.5), sodium 131 mmol/L (135-148), and potassium 5.7 mmol/L (3.5-5.3). Chest x-ray showed increased interstitial infiltrates in both lung bases. Hemodialysis and transfusion of packed cells and platelets were instituted. On the second hospital day, endoscopy revealed erosion and bleeding in the antrum and a bleeding tumor was found at the main duodenal papilla (Fig. 1); biopsies were obtained. On the third hospital day, he developed worsening respiratory distress without fever. Cefotetan was given pending results of blood and urine cultures and histopathologic evaluation of the biopsies. He became obtunded, was intubated for ventilator support because of respiratory failure and hypotension and was admitted to the intensive care unit. Despite the use of inotropic agents and resuscitation with intravenous fluids, hypotension ensued followed by ventricular arrhythmia. Cardiopulmonary resuscitation restored normal sinus rhythm. He became comatose thereafter and his family requested no further therapy. He was discharged against medical advice on the fourth day, intubated and on inotropic agents. Histopathologic evaluation of the biopsies disclosed ulceration with an inflammatory cell infiltrate, focal papillary hyperplasia, and yeastlike organisms inside histiocytes with hematoxylin and eosin staining and septated yeasts with Gomori-methenamine silver (GMS) stain (Fig. 2), consistent with *P marneffei*. Blood cultures subsequently yielded *P marneffei* 1 week after death.

Case 2

A 52-year-old man was admitted because of intermittent fever, watery diarrhea, and abdominal pain for 3 weeks. He was diagnosed with AIDS three years earlier and had lived in Canton Province of China for 10 years. He

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Figure 1. Endoscopic appearance of a bleeding tumor at the main duodenal papilla.

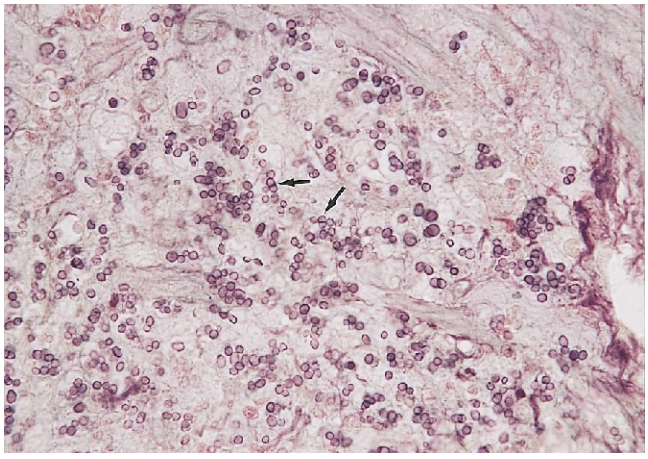

Figure 2. Microscopic appearance of a biopsy from the lesion in Figure 1 revealing septated yeast (*arrow*) inside histiocytes (Gomori-methenamine silver stain; orig. mag. ×400), a finding characteristic of *Penicillium marneffei*.

had been treated with trimethoprim-sulfamethoxazole, zidovudine and didanosine. Physical examination revealed a pale, feverish patient with a 1 × 0.5 cm erupted papule in the infraclavicular area. The liver was slightly enlarged. Ophthalmologic examination revealed findings consistent with cytomegalovirus retinitis. The rest of physical examination was normal. Hemoglobin was 7.2 gm/dL and white blood cell count 2.92 k/mm^3 with 65.7% neutrophils. CD4 count was 20/mm^3. Abnormal biochemistry tests (normal values in parentheses) were albumin 2.8 gm/dL (3.5-5.0); aspartate aminotransferase 50 U/L (<37); alkaline phosphatase 385 U/L (67-238); γ-glutamyl transferase 171 U/L (<52); lactate dehydrogenase 548 U/L (230-460); amylase 151 U/L (<220); lipase 320 U/L (<190). Stool examinations of occult blood and parasite ova were nondiagnostic.

Barium enema showed a disorganized mucosa pattern with a mass effect at the terminal ileum. Colonoscopy revealed an 0.3 cm shallow cecal ulcer beside the ileocecal valve with edema and petechiae over the ileocecal valve

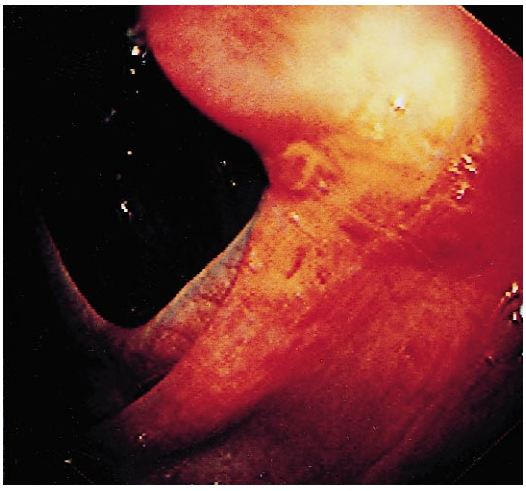

Figure 3. Colonoscopic appearance of a shallow cecal ulcer in a patient with AIDS due to colonic penicilliosis marneffei.

(Fig. 3). The mucosa of the rest of the colon appeared normal. Histopathologic evaluation of biopsies from the ulcer showed diffuse histiocytic infiltrates with numerous intracellular yeast cells in the mucosa and lamina propria. GMS and periodic acid-Schiff stains demonstrated scattered round to sausagelike fungi with central septation that were consistent with *P marneffei*. Cultures of blood, bone marrow and skin all subsequently yielded *P marneffei*. Amphotericin B was given at a daily dose of 1 mg/kg for 2 weeks followed by itraconazole at a daily dose of 400 mg for maintenance therapy. He had no recurrence of bowel or systemic symptoms.

Case 3

A 30-year-old Chinese man from Thailand presented with dyspepsia, intermittent abdominal cramping pain and watery diarrhea for 2 months prior to admission. He also developed intermittent fever, bloody stool and a weight loss of 6 kg. Physical examination revealed a pale and emaciated patient with mild tenderness in the left lower abdomen. Liver and spleen were not enlarged. Hemoglobin was 10.5 gm/dL and white blood cell count was 4.34 k/mm^3 with 54% neutrophils and 15% lymphocytes. Results of routine biochemical tests were normal except for serum albumin of 3.0 gm/dL. A test for antibody to HIV was positive. The stool contained no blood or mucus and microscopic examinations for parasites were negative. CT of abdomen showed mesenteric lymphadenopathy and edematous small intestine. Colonoscopy revealed multiple solitary shallow ulcers with and without elevated margins in the cecum, ascending and transverse colons. The mucosa of the rest of the colon appeared normal. Biopsies from the ulcers showed mucosal ulceration and infiltration of the lamina propria and mucosa by mononuclear cells, eosinophils, and markedly distended histiocytes laden with yeastlike microorganisms, suggestive of *H capsulatum* or *P marneffei*. GMS stain showed central septation of yeasts. Culture of the blood yielded *P marneffei*. Culture of bone marrow showed no growth of fungi. The patient was given amphotericin B

Table 1. Summary of clinical characteristics of 7 cases of intestinal penicilliosis marneffei

Case [reference]	Age (yr)/ gender	Area of report	Underlying disease/ medications	Clinical presentations	Involved organ or tissue (diagnostic methods)*	Endoscopic findings	Treatment/ maintenance†	Outcome
1 [8]	0.33/M	China	NM	Fever, diarrhea, anemia, lymphadenopathy, hepatosplenomegaly	Lymph nodes, liver, lung, bone marrow spleen, bowel, kidney (A)	ND	None	Died
2 [9]	58/M	Hong Kong	Hemolytic anemia/ steroids	Fever, anemia, hepatosplenomegaly	Descending colon (C+H); liver, lung (A)	ND	Amphotericin B	Died
3 [12]	72/M	Hong Kong	AIDS	Anorexia, dysphagia, weight loss, GI bleeding	Small intestine (B+C); mesenteric lymph node, liver (A)	ND	NM	Died
4 [17]	32/M	Hong Kong	AIDS	Fever, diarrhea, night sweats, dry cough	Cecum, transverse and descending colon (B+C)	Multiple solitary ulcers	Amphotericin B/ itraconazole	Survived
5 [PR]	33/M	Taiwan	Renal transplant recipient/ cyclosporine, azathioprine, steroids, tacrolimus	Fever, diarrhea, septic shock, duodenal tumor with bleeding	Duodenum (B)	Erosion at antrum and ampulla Vater tumor with bleeding	None	Died
6 [PR]	52/M	Taiwan	AIDS	Fever, diarrhea, anemia, abdominal pain	Skin, bone marrow (B+C); colon (B)	Shallow ulcers	Amphotericin B/ itraconazole	Survived
7 [PR]	30/M	Taiwan	AIDS	Dyspepsia, diarrhea, fever, abdominal pain, bloody stool, weight loss	Cecum, ascending and transverse colons (B)	Shallow ulcers	Amphotericin B/ itraconazole	Survived

ND, Not done; *NM*, not mentioned; *PR*, present report.

*Diagnostic methods to demonstrate *P marneffei* were autopsy (*A*), biopsy (*B*), culture (*C*) or histopathology (*H*).

†Case 2 developed peritonitis after receiving amphotericin B for 4 days and died after surgical treatment. Case 4 received amphotericin B with a cumulative dose of 650 mg and maintenance therapy with itraconazole 400 mg/day. Cases 6 and 7 received amphotericin B with a daily dose of 1 mg/kg for 2 weeks and maintenance therapy with itraconazole 400 mg/day.

at a daily dose of 1 mg/kg for 2 weeks. Diarrhea, abdominal pain and fever resolved promptly. Colonoscopy after 2 weeks of therapy revealed only two healing ulcers over the ileocecal valve; the rest of the colonic mucosa was normal. Colonic biopsies demonstrated complete clearance of yeast in the colonic mucosa. The patient was maintained on oral itraconazole at a daily dose of 400 mg and had no recurrence of symptoms.

DISCUSSION

P marneffei can infect both healthy and immunocompromised individuals but the majority of the cases are reported in patients with AIDS in areas where the organism is endemic.[5-17] In renal transplant recipients receiving immunosuppressive therapy, only one previous case of penicilliosis marneffei has been reported.[18] The most common manifestations of disseminated penicilliosis marneffei in patients with AIDS are fever, anemia, weight loss and skin lesions. GI symptoms associated with penicilliosis marneffei are relatively common.[14] Diarrhea was present in 31% of patients with AIDS and disseminated penicilliosis marneffei in a series of 92 patients from Thailand[14] and in 23.2% of cases in another review of 155 HIV- and non-HIV-infected patients.[16] Despite the frequency of GI symptoms, histopathologic documentation of GI involvement with penicilliosis marneffei has rarely been described.[8,9,12,15,17]

Including the 3 cases in the present report, intestinal penicilliosis marneffei has been diagnosed in 7 patients by histopathology or culture of intestinal tissues (Table 1).[8,9,12,17] Intestinal involvement in cases of disseminated penicilliosis may have been underdiagnosed because the diagnostic yield of cultures of blood, bone marrow, and skin are high enough to have rendered investigation of intestinal tract by endoscopy unnecessary. In contrast to diagnostic yields of 76%, 90%, and 100% for cultures of blood, skin biopsy, and bone marrow aspirate,[14] respectively, the organism has been infrequently isolated from stool cultures. Only 6 cases with positive stool cultures for *P marneffei* have been documented.[5,7,10-13] The significance of positive stool cultures remains unclear, however, because in none of these cases was there histopathologic evidence of intestinal penicilliosis.

GI tract involvement by disseminated penicilliosis marneffei may range from esophagus[15] to colon (Table 1).[8,9,12,17] Endoscopic findings include shallow ulcers that are not easily differentiated from those of intestinal histoplasmosis.[4] In this report, we described another endoscopic finding of intestinal penicilliosis marneffei, a bleeding tumor of the main duodenal papilla, that has not been described previously. Histopathologic examination of specimens from the margins of the ulcers often discloses lymphocytes and histiocytes distended with yeasts. Microscopically, it is difficult to differentiate intrahistiocytic yeast cells of *P marneffei* from those of *H capsulatum*; outside of the histiocytes, the former shows much more variation in morphology than the latter.[6] The demonstration of characteristic central septation and elongated sausage-shaped forms by GMS stain, and the absence of buds attached by a narrow neck clearly distinguish *P marneffei* from *H capsulatum*.[6]

The mortality rate for patients with *P marneffei* infection is extremely high; the reported rate for untreated HIV-infected patients with disseminated penicilliosis marneffei was 75%.[19] Delay in diagnosis and treatment is the most likely explanation for the high mortality rate, therapy often being delayed while awaiting microbiologic results for 1 or 2 weeks.[13] The diagnosis of intestinal penicilliosis marneffei as part of the presentation of disseminated penicilliosis may not be made until autopsy (Table 1). In our patients the diagnosis was made by endoscopy earlier than was possible by relying on conventional microbiologic cultures and led to successful therapy in 2 patients with AIDS although the patient who underwent renal transplantation died before antifungal therapy could be instituted.

Intestinal penicilliosis marneffei should be included in the differential diagnosis of diarrhea and fever in immunocompromised hosts who are visitors to or residents of endemic areas. Performance of endoscopy to obtain tissue specimens for histopathology and culture may lead to earlier diagnosis and improve survival.

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