CASE SERIES

FUNGAL APPENDICITIS: A CASE SERIES AND REVIEW OF THE LITERATURE

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Abstract. Appendicitis is a condition characterized by inflammation of the vermiform appendix, which is commonly caused by bacterial infections and rarely caused by fungal organisms. In the present study, we reviewed the prevalence, clinicopathological features, and therapeutic management of fungal appendicitis. During July 2010 to June 2011, the pathology of 262 resected vermiform appendices was reviewed. Fungal appendicitis occurred in 1.15%, including two cases of *Candida* spp and one case of *Aspergillus* spp infection. All patients were immunocompromised and presented with the classical signs and symptoms of appendicitis with the onset of illness less than two days. They were considered for acute appendicitis and underwent appendectomy. The histopathology of the resected vermiform appendix showed fungal organisms with suppurative inflammation and secondary periappendiceal peritonitis. The curative treatment was presented in 1-out-of-3 cases. One patient was alive during a follow-up of eight months. Two patients died, and an autopsy was performed in one case. Although fungal appendicitis was uncommon, the disease might occur among immunosuppressed patients who have developed classical signs and symptoms of appendicitis. Early diagnosis and prompt surgery with medical treatment are associated with a survival advantage.

Keywords: aspergillosis, candidiasis, fungal infection, mycosis, vermiform appendix

INTRODUCTION

Appendicitis is a condition characterized by inflammation of the vermiform appendix. It is one of the best-known medical entities and is the most common condition requiring emergency abdominal surgery. Although the possible etiology of appendicitis is multifactorial, the exact cause of appendicitis remains unknown, but the two most likely causes are thought to be infection and luminal obstruction.

Between types of causative patho-

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gens, bacteria outweigh fungus as the predominant cause of infectious-related appendicitis. Fungal appendicitis is an uncommon disease. The definite diagnosis largely relies on appendectomy specimens with a histopathologic confirmation of fungal organism. At present, there are little epidemiological data regarding fungal appendicitis.

Fungal infection is a major problem in an era of a growing number of immunocompromised populations and is often clinically mistaken for bacterial infection, with fatal consequence. However, the prevalence and incidence of fungal appendicitis is low (Lamps, 2004, 2010; Akbulut *et al*, 2011). Among non-AIDS patients who developed systemic mycosis, the fungal appendicitis occurs in 0.65% of autopsy cases (Larbcharoensub *et al*, 2007).

In this paper, the authors present three cases of histopathologically verified fungal appendicitis seen at a tertiary care center in Thailand.

CASE SERIES

This was a retrospective study of fungal appendicitis diagnosed on histopathologic materials from the Department of Pathology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, during July 2010 to June 2011. All cases were seronegative for human immunodeficiency virus (HIV).

The vermiform appendix was formalin-fixed and routinely processed for paraffin embedding. A tissue section, 4 m thick, was cut. Routine hematoxylin and eosin (H&E)-stained sections were examined for histopathologic findings. Fungal morphology was delineated using special stains, ie, Gomori-Grocott methenamine silver (GMS), and periodic acid Schiff (PAS). The histopathological diagnosis of invasive fungal appendicitis was reviewed. Information obtained from the medical records including age, gender, underlying predisposing risk factors for the disease, clinical manifestations, and microbiologic study were analyzed.

The present study was approved by the Committee on Human Rights Related to Researches Involving Human Subjects at the Faculty of Medicine Ramathibodi Hospital, Mahidol University (ID06-54-34, 2011 July 4).

Case 1

A 5-year-old girl presented with one day of right lower quadrant abdominal pain and fever. The patient's past medical history was significant for diffuse large B-cell lymphoma of the central nervous system and acute promyelocytic leukemia (M3), and was started on six cycles of chemotherapy according to a protocol of Thai Pediatric Oncology Group (ThaiPOG, 2008). She developed febrile neutropenia. Serum galactomannan was positive. Invasive pulmonary aspergillosis (IPA) was diagnosed.

She was treated with intravenous amphotericin B and voriconazole, followed by oral itraconazole, 400 mg daily. Two days prior to this admission, she remained neutropenia and developed right lower quadrant abdominal pain, fever, anorexia, nausea, and vomiting. Computed tomography (CT) of the abdomen and pelvis showed early abscess formation at superior aspect of the distal ileum and vermiform appendix. She was taken for an open appendectomy.

The pathological diagnosis was fungal appendicitis caused by invasive aspergillosis (Fig 1). Intravenous amphotericin B, metronidazole, and piperacillin with tazobactam were given. However, one day after the operation, she finally succumbed

to the disease with the diagnosis of septicemia with disseminated intravascular coagulopathy. Hemoculture for fungal organism showed no growth. Autopsy disclosed disseminated fungal infection involving brain, lungs, heart, small intestine, large intestine, liver, spleen, kidneys, right ovary, and urinary bladder.

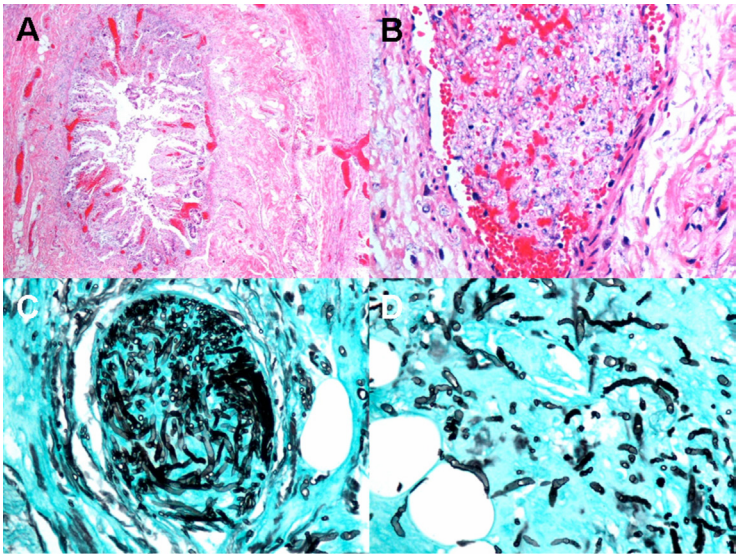

Fig 1–A section of acute appendicitis with lymphoid depletion (A, H&E, x20), fungal organisms in vascular lumen (B, H&E, x400; C, GMS, x400), and fungal organisms infiltrating in appendiceal subserosa (D, GMS, x400).

Case 2

A 33-year-old Thai female teacher presented with one day of right lower quadrant abdominal pain. On examination, her abdomen was mildly tender on palpation. The past medical history was significant for acute lymphoblastic leukemia with complex chromosomal abnormalities for which she was started on two cycles of hyper CVAD chemotherapy, including cyclophosphamide, vincristine, doxorubicin, and dexamethasone. She developed febrile neutropenia and acute kidney injury.

One day prior to this admission, she developed right lower quadrant abdominal pain, fever, anorexia, nausea, and vomiting. A CT of the lower abdomen showed diffuse appendiceal wall enhancement without focal-wall destruction associated with periappendiceal fat reticulation, suggestive of acute appendicitis with secondary inflammation (Fig 2). She was taken for an open appendectomy.

Fungal appendicitis caused by mucosal and invasive *Candida* spp was diagnosed. She was treated with intravenous ceftazidime, metronidazole, amphotericin B, and oral fluconazole, 400 mg daily. Hemoculture grew *Acinetobacter baumannii*. Serum galactomannan was negative. Finally, she expired at 41 days after the operation with the diagnosis of bacterial septicemia and adult respiratory distress syndrome. No autopsy was performed.

Case 3

A 45-year-old Thai female was admitted to Ramathibodi Hospital because of fever, right lower quadrant abdominal pain, anorexia, nausea, and vomiting of two days' duration. The past medical history was significant for acute myeloid leukemia (M4) with inv (16)(p13.1q22), for which she was started on idarubicin/ara-C regimen for two cycles. She had a history of febrile neutropenia.

On physical examination, her lower abdomen was markedly tender on palpation and positive for rebound tenderness. A CT abdomen showed enlargement with enhancing thicken wall of vermiform ap-

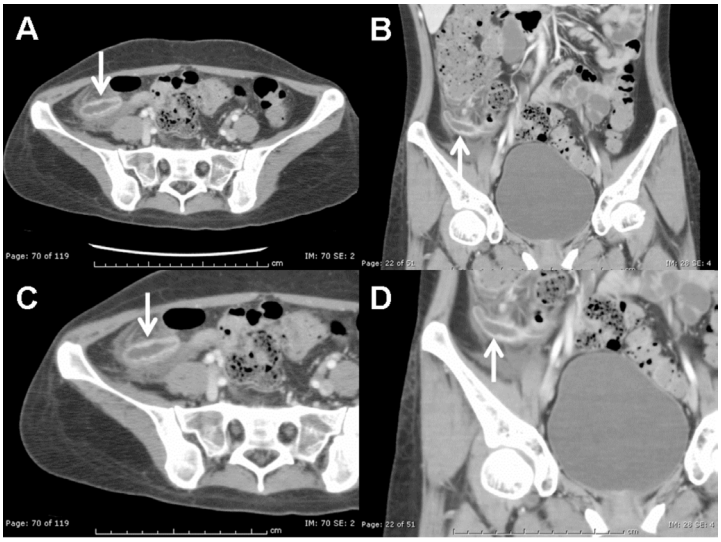

Fig 2–CT abdomen demonstrates a thick and enhanced wall vermiform appendix (arrow) with fluid-filled lumen, measuring 11 mm in diameter. There is associated moderate periappendiceal fat reticulation, fascial thickening and secondary inflammation of the terminal ileum. Minimal free fluid is noted. (A, Non-contrast axial CT; B, non-contrast coronal CT; C, post-contrast axial CT; D, post-contrast coronal CT).

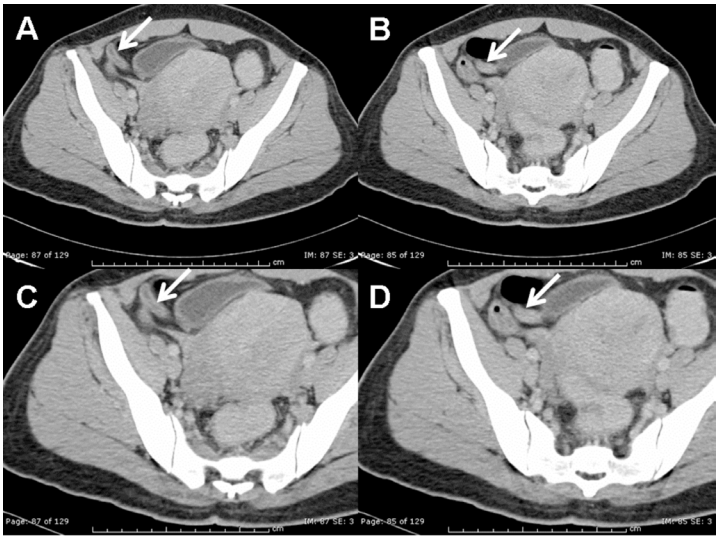

Fig 3–CT abdomen demonstrates a thickened and enhanced wall vermiform appendix (arrow), measuring 9 mm in diameter. There is mild periappendiceal fat reticulation and fascial thickening. A, B, non-contrast axial CT; C, D, post-contrast axial CT.

pendix and mild periappendiceal fat reticulation without evidence of wall disruption, suggestive of early acute appendicitis (Fig 3). Open appendectomy was performed.

Postoperative intravenous metronidazole and piperacillin with tazobactam were given. The postoperative course was uneventful. The pathological diagnosis was fungal appendicitis caused by mucosal and invasive *Candida* spp. Hemoculture for fungal organism showed no growth. Serum galactomannan was positive. Systemic workup revealed invasive fungal sinusitis and IPA. Tissue culture of the maxillary sinus grew *Aspergillus fumigatus*. Multiple liver abscesses were detected. The liver aspiration revealed budding yeasts with pseudohyphae.

She was treated with intravenous amphotericin B and switched to oral voriconazole. The pulmonary and spinal lesions resolved with antifungal treatment. However, progression of microabscesses of the liver was detected. Intravenous micafungin in combination with oral voriconazole were given. The clinical finding and hepatic lesion were improving. She

was discharged and continued received oral voriconazole. Her condition remains healthy at eight months after appendectomy. The scheduled chemotherapy was continued.

Summary of cases

The authors reviewed the pathology of 262 vermiform appendices resected over the past one year. Only three cases of fungal appendicitis were recognized. The overall prevalence of fungal appendicitis was 1.15%. All patients were female and presented with fever and abdominal pain. The onset of symptoms ranged from one to two days. The ages of patients ranged from 5-45 years, with the mean and median ages of 27.7 and 33 years, respectively (Table 1).

They were considered for acute appendicitis and underwent appendectomies. The histopathology of the resected vermiform appendix showed fungal organisms with suppurative inflammation and secondary periappendiceal peritonitis. Hemoculture for fungal organism from all patients revealed no growth. Serial serum galactomannan enzyme immunoassay (GM-EIA; Platelia ™ *Aspergillus* EIA; Bio-Rad, Hercules, CA) was positive in two cases (Patients No. 1 and 3).

Clinical management depended on the clinical situation of individual cases. The antifungal drugs were given in all three cases. The curative treatment was presented in 1-out-of-3 cases (Patient No. 3). This patient was alive during a follow-up of 8 months. Two patients (Patients No. 1 and 2) died of disseminated fungal septicemia. The autopsy was performed on one case (Patient No. 1) and showed systemic fungal infection involving brain, lungs, heart, small intestine, large intestine, liver, spleen, kidneys, right ovary, and urinary bladder.

DISCUSSION

Vermiform appendiceal infection most frequently is caused by local bacterial infection. Fungal infection is an uncommon disease of vermiform appendix. The importance of fungal infections of the vermiform appendix has increased as the numbers of patients with immunosuppression and organ transplantation have risen. Appendicitis in immunosuppressed patients has high mortality and complication rates. Immunosuppressive drugs impair the inflammatory processes and suppress white blood cell responses, which increases the risk of developing appendicitis. Information regarding its clinical and pathological features is limited. Appendiceal fungal infections caused by mucormycosis, histoplasmosis, South American blastomycosis, aspergillosis, and candidiasis have been reported (Christopherson *et al*, 1952; Rogers *et al*, 1990; ter Borg *et al*, 1990; Sasaki *et al*, 1996; Nichol *et al*, 2004; Karanth *et al*, 2005; Wiegering *et al*, 2008; Khoury *et al*, 2010). However, most of them were single-case reports.

Fungal appendicitis has a wide spectrum of clinical manifestations including abdominal pain, anorexia, nausea, vomiting, and fever. The duration of these presenting symptoms is highly variable, ranging from one hour to one day (Wiegering *et al*, 2008). Most patients have symptoms, clinical signs, and laboratory and radiological features resembling bacterial appendicitis. A high index of suspicion is therefore very essential, especially in immune-depleted cases. Underlying hematologic malignancy being treated by chemotherapy, which causes febrile neutropenia is the commonest underling disease.

The diagnosis of fungal appendicitis

Table 1
Clinical and pathological findings of 3 patients with fungal appendicitis.

	Patient no.		
	1	2	3
Age (years)	5	33	45
Sex	Female	Female	Female
Chief complaint	Fever, and abdominal pain for 1 day	Fever, and abdominal pain for 1 day	Fever, and abdominal pain for 2 days
Underlying disease	Diffuse large B-cell lymphoma of the central nervous system Acute myeloid leukemia, M3 Invasive pulmonary aspergillosis	Acute lymphoblastic leukemia	Acute myeloid leukemia, M4 Invasive fungal sinusitis and invasive pulmonary aspergillosis
Length of vermiform appendix (cm)	3.5	5	5
Diameter of vermiform appendix (cm)	0.5	1.2	1
Ruptured site	Not seen	Not seen	Not seen
Histopathologic diagnosis of fungal organism in vermiform appendix	*Aspergillus* spp	*Candida* spp	*Candida* spp
Serum galactomannan ELISA	Positive	Negative	Positive
Hemoculture for fungal organism	No growth	No growth	No growth
Treatment	Appendectomy	Appendectomy	Appendectomy
Antifungal agent	Amphotericin B, voriconazole, itraconazole	Amphotericin B, fluconazole	Amphotericin B, micafungin, voriconazole
Status	Death 1 day after appendectomy	Death 41 days after appendectomy	Alive 8 months after diagnosis
Autopsy finding	Disseminated fungal infection, involving brain, lungs, heart, small intestine, large intestine, liver, spleen, kidneys, right ovary and urinary bladder	Not performed	Alive

cannot be made by clinical and radiological manifestations but can only be judged by histopathologic demonstration of fungal element and tissue reaction. Fungal infection typically results in a localized inflammatory cell infiltrate. The fungal pathogen usually locates at appendiceal mucosa or in periappendiceal vessels, depending on the pathogenesis of disease.

Secondary direct invasion of fungal pathogen into appendiceal tissue is the possible cause of fungal appendicitis. Peritonitis typically occurs in extensive destruction of vermiform appendix by fungal organisms. The early stage of destruction typically presents as right lower abdominal pain. Generalized abdominal pain is typically presented in the advance stage of the disease.

The postulated pathogeneses of fungal appendicitis include intravascular dissemination secondary from systemic fungal infection and the locally invasive nature of intraluminal fungal organism. Fungal appendicitis usually occurs in patients with immunosuppression and organ transplantation; therefore, mucosal associated lymphoid tissue (MALT) typically shows lymphoid depletion. Reactive lymphoid hyperplasia with secondary luminal obstruction in the inflamed vermiform appendix is the less likely pathogenesis of fungal appendicitis, unlike bacterial appendicitis. However, synchronous bacterial and fungal infections may be an additional possible pathogenesis of fungal appendicitis.

Aspergillus spp infection of the gastrointestinal tract occurs almost exclusively in immunocompromised patients (Rogers *et al*, 1990; Bömelburg *et al*, 1992; Lehrnbecher *et al*, 2006; Park *et al*, 2010). Aspergillus appendicitis may be complicated by systemic aspergillosis. The majority of patients with aspergillus appendicitis have coexistent pulmonary lesions. The vermiform appendix is frequently involved in this setting due to the lymphoid depletion that is typically found in immunosuppressed patients.

Systemic aspergillosis shows the angioinvasive nature of intravascular thrombosis, and ischemic necrosis in early and hemorrhagic infarction in later stages. Minimally inflammatory response has occurred. The diagnosis of fungal appendicitis depends on the presence of typical hyphae in the tissue. Using the GMS procedure, fungal hyphae may be easily detected in area of suppurative inflammation that is observed in appendectomy specimen.

Candida spp are part of the normal flora in the gastrointestinal tract. However, some *Candida* spp can become pathogenic, especially in immunosuppressed patients, as presented in our last two cases. *Candida* spp is the most common infection of the esophagus, but it may infect any level of the gastrointestinal tract, including vermiform appendix (Khoury *et al*, 2010). *Candida* spp typically directly invades the epithelial cells and spreads to multiple organs via the portal system causing fungemia and systemic fungal infection. The gross features of candidiasis include ulceration, pseudomembrane formation and inflammatory masses.

If vascular invasion is prominent, the gastrointestinal tract may appear infarcted. The histopathology findings range from minimal to marked prominent inflammatory cells infiltration, abscess formation, erosion or ulceration, and necrosis, depended on immunologic status of the patients. Granulomatous inflammation is occasionally present.

The differential diagnoses of fun-

gal infection include other infectious processes and occasionally Crohn's disease, ulcerative colitis, sarcoidosis, and ischemic colitis. The authors emphasize the importance of histopathologically studying appendiceal specimens for the diagnosis of mycosis, and in particular, for the differential diagnosis of appendicitis. Clinical and pathological correlations are essential. Recent diagnostic tools, including serum galactomannan enzyme-linked immunosorbent assay (ELISA), and polymerase chain reaction (PCR) for fungal pathogens, provide the opportunity to consider earlier the diagnosis of fungal infection.

Appendectomy is recommended for symptomatic acute appendicitis. Fungal appendicitis should be medically treating as disseminated fungal infection. Patients should be treated initially with amphotericin B at a dosage of 0.7 to 1 mg/kg daily or lipid formulation of amphotericin B at a dosage of 3 to 5 mg/kg daily. Continuing amphotericin B throughout the entire course of therapy is no longer the standard of care. For almost all patients, as their condition improves, generally within a few weeks, their therapy is switched to oral voriconazole at a dosage of 200 mg twice daily (Lehrnbecher *et al*, 2006). Intravenous micafungin with oral voriconazole are recommended as alternative treatment of appendiceal candidiasis. The patient was successfully treated with early appendectomy in combination with antifungal therapy.

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