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**Characteristic clinical features of Aspergillus appendicitis: Case report and literature review**

Gjeorgjievski M *et al*. Aspergillus appendicitis associated with neutropenia and AML

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**Abstract**

This work aims to facilitatediagnosing Aspergillus appendicitis, which can be missed clinically due to its rarity, by proposing a clinical pentad for Aspergillus appendicitis based on literature review and one new case. The currently reported case of pathologically-proven Aspergillus appendicitis was identified by computerized search of pathology database at William Beaumont Hospital, 1999-2014. Prior cases were identified by computerized literature search. Among 10980 pathology reports of pathologically-proven appendicitis, one case of Aspergillus appendicitis was identified (rate = 0.01%). A young boy with profound neutropenia, recent chemotherapy, and acute myelogenous leukemia presented with right lower quadrant pain, pyrexia, and generalized malaise. Abdominal-computed tomography scan showed a thickened appendiceal wall and periappendiceal inflammation, suggesting appendicitis. Emergent laparotomy showed an inflamed, thickened appendix, which was resected. The patient did poorly postoperatively with low-grade-fevers while receiving antibacterial therapy, but rapidly improved after initiating amphotericin therapy. Microscopic examination of a silver-stain of the appendectomy specimen revealed fungi with characteristic Aspergillus morphology, findings confirmed by immunohistochemistry. Primary Aspergillus appendicitis is exceptionally rare, with only 3 previously reported cases. All three cases presented with neutropenia, recent chemotherapy, acute leukemia, and suspected appendicitis; the two prior cases initially treated with antibacterial therapy fared poorly before instituting anti-Aspergillus therapy. The current patient satisfied all these five criteria. Based on these four cases, a clinical pentad is proposed for Aspergillus appendicitis: clinically-suspected appendicitis, neutropenia, recent chemotherapy, acute leukemia, and poor clinical response if treated solely by antibacterial/anti-candidial therapy. Patients with this proposed pentad may benefit from testing for Aspergillus infection by silver-stains/immunohistochemistry and considering empirical anti-Aspergillus therapy pending a tissue diagnosis.

**Key words**: Aspergillosis; Aspergillus appendicitis; Fungal appendicitis; Appendicitis; Neutropenia; Chemotherapy; Acute myelocytic leukemia

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**Core tip:** This work reports the fourth reported case of isolated Aspergillus appendicitis, further characterizes this syndrome, and identifies a clinical pentad associated with this syndrome: clinically-suspected appendicitis, neutropenia, recent chemotherapy, acute leukemia, and poor clinical course if treated solely with antibacterial or anti-Candidial antibiotics. These risk factors are biologically reasonable. Immunosuppression from neutropenia and acute leukemia may promote Aspergillus appendicitis. Local gastrointestinal ulcers from recent chemotherapy provides a nidus for fungal colonization. In patients presenting with this proposed pentad, Aspergillus appendicitis should be considered in the differential diagnosis, special silver stains should be performed to evaluate for this infection, and empiric anti-Aspergillus therapy may be considered pending tissue diagnosis.

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**Introduction**

The diagnosis of isolated (primary) Aspergillus appendicitis may be clinically overlooked or delayed because of its exceptional rarity, as shown by a review of the English literature revealing only three cases, and its association with profound immunosuppression (Table 1)[1-3] that can delay or mask the usual clinical features of appendicitis[4,5]. Yet, delayed diagnosis and therapy for Aspergillus appendicitis may have dire patient consequences, as occurred in two of the three previously reported cases[1,2]. A new patient is reported of isolated Aspergillus appendicitis who presented with five striking clinical findings, and a novel syndromic pentad is proposed as a diagnostic tool, based on this new case report and review of the three previously reported cases that demonstrated nearly identical findings.

Computerized search using the words “appendicitis” and “Aspergillus” of the pathology database at William Beaumont Hospital, Royal Oak, July 1999-December 2014, revealed only 1 case of Aspergillus appendicitis (0.01% rate) among 10,980 pathology reports of appendicitis proven by pathologic examination of the appendectomy specimen. Published reports of Aspergillus appendicitis were identified by computerized literature search using PubMed; and review of general textbooks and specialized monographs in gastroenterology, pathology, and infectious diseases. One case report of isolated Aspergillus appendicitis written in German was professionally translated[6]. Case reports of small intestinal Aspergillosis without known or documented appendiceal involvement were excluded[7]. This study received exemption/approval by William Beaumont Hospital IRB on December 1, 2014.

**Case report**

An 8-year-old boy with acute myelogenous leukemia (AML), diagnosed one month earlier, and with profound neutropenia, after receiving two cycles of IV chemotherapy with daunorubicin, cytarabine, thioguanine, etoposide and dexamethasone, presented with low-grade pyrexia and chills for one day. Physical examination revealed temperature = 36.8 0C, pulse = 111 beats/min, blood pressure = 94/63 mmHg. and mild right lower quadrant (RLQ) tenderness without rebound tenderness. The leukocyte count = 200 cells/mm3 (normal 4800-10100 cells/mm3), neutrophil count < 100 cells/mm3 (normal 1600-7200 cells/mm3), hematocrit = 36.3% (normal in male boy, age 6-9 years: 33.6%-43.4%), and platelet count = 90000/mm3 (normal 150000-400000/mm3). Abdominal ultrasound was unrevealing. Abdomino-pelvic computed tomography (CT) showed a mildly enlarged appendix without an appendicolith or periappendiceal inflammation, findings possibly consistent with early appendicitis. The patient was rehydrated with normal saline and administered IV antibiotic therapy with amoxicillin, gentamicin and metronidazole, but developed increasing RLQ abdominal pain and several episodes of vomiting during the ensuing 24 h. Repeat abdomino-pelvic CT scan revealed a dilated appendiceal lumen, thickened appendiceal wall, and periappendiceal fat stranding, findings consistent with appendicitis (Figure 1).

Emergency laparotomy revealed an inflamed, edematous, dusky appendix without appendiceal perforation but with thickened periappendiceal mesentery. The appendix was resected. Microscopic examination of hematoxylin and eosin stains of histologic sections of the resected appendix showed an acute necrotizing appendicitis, with scattered questionable fungal hyphal forms. Postoperatively, the patient continued to be ill with persistent moderate pyrexia for 12 d, while receiving IV ampicillin, gentamicin, and metronidazole antibiotic therapy and filgrastim (granulocyte colony stimulating factor). Due to this poor clinical response, evident risk factors for fungal appendicitis, and questionable findings of fungal hyphae on a conventional hematologic stain, a Grocott-Gomori methenamine-silver nitrate stain was performed on the resected specimen which revealed numerous fungal hyphae that showed features characteristic of Aspergillus of septation and acutely angled branching, and which was confirmed as Aspergillus by immunohistochemistry (Figure 2A, B). The specific species causing the Aspergillus infection could not be determined in the formalin fixed tissue. On day 13 IV amphotericin-B was added to the antibiotic regimen and the patient rapidly improved clinically, with defervescence and gradual recovery of the leukocyte count to 3400 cells/mm3. He was discharged after 21 d of IV amphotericin therapy to receive oral itraconazole as an outpatient. During 8 months of follow up, the patient had 2 relapses of AML, but no evident Aspergillus recurrence, while continuing oral antifungal prophylaxis with itraconazole.

**Discussion**

Aspergillus, a widespread fungus in the environment, usually enters the human body by airborne transmission and colonizes the nasal cavities or facial sinuses. Invasive pulmonary aspergillosis accounts for 90%-98% of invasive Aspergillus infections, but hematogenous spread may cause disseminated infection[8-12], or rarely isolated infections of other organs, including central nervous system, heart, liver, kidneys, and gastrointestinal (GI) tract[13-17]. Based on a literature review of more than 3000 cases of Aspergillus infection, Denning et al. hypothesized that isolated GI aspergillosis generally arises from ingestion of food contaminated with Aspergillus, and colonization by Aspergillus of GI ulcers which can arise from antecedent chemotherapy[10,18].

Aspergillus fumigatus is the most frequent species that causes human infections, followed by A. flavus, A. terreus, A. niger, and A. nidulans[19]. The risk of pulmonary infection and hematogenous spread greatly increases with immunosuppression, including profound neutropenia, glucocorticoid therapy, and neutrophilic or phagocytic dysfunction from acute leukemia[20,21], chronic granulomatous disease, and advanced human immunodeficiency virus infection[7,22-24].

GI aspergillosis is rare[7,22,25], isolated GI aspergillosis is even rarer, and isolated Aspergillus appendicitis is exceedingly rare. For example, in a review of 1,538 patients with aspergillosis, only 85 (5.5%) had GI aspergillosis, and only 14 (0.8%) patients had isolated GI aspergillosis[7].The currently reported case of isolated appendiceal aspergillosis represents only the fourth reported case in the English literature (Table 1). A fifth case published in German in 1959[6] is detailed in Table 1, but not presently analyzed because (1) it was published before the advent of modern laboratory and imaging tests for appendicitis, such as abdominal ultrasound or CT; and (2) the case report lacked critical clinical details, such as microscopic findings, due to brevity of the report.

All four analyzed cases, including the current case, presented with a distinct syndrome of clinically-suspected appendicitis, acute leukemia [either AML or acute lymphocytic leukemia (ALL)], recently administered chemotherapy, and neutropenia (Table 1)[1-3]; and three of the patients, including the current case, initially did poorly when receiving antibacterial therapy without anti-Aspergillus therapy[1,2]. The fourth case received anti-Aspergillus therapy promptly without delay. Four other cases of appendiceal aspergillosis were reported with other GI involvement, but without clinically apparent extraintestinal spread (Table 2)[26-29], of which one had disseminated aspergillosis demonstrated by autopsy[29]. All four of these cases, like the four cases of isolated Aspergillus appendicitis, had underlying AML or ALL, neutropenia, and recent chemotherapy.

To promote early diagnosis and appropriate treatment, a clinical pentad is proposed for suspected Aspergillus appendicitis of: (1) clinically-suspected appendicitis; (2) neutropenia; (3) recent chemotherapy; (4) underlying acute leukemia; and (5) poor response if administered antibacterial antibiotics or anti-Candidial therapy without anti-Aspergillus therapy. The hypothesized pathophysiology of the proposed syndromic pentad is Aspergillus, presumably ingested in contaminated food (1) colonizes GI ulcers or areas of mucositis induced by chemotherapy. Mucosal ulcers commonly occurs after chemotherapy with daunorubicine, which was administered in 3 of the 4 reported cases[2,3,current report], or after chemotherapy with cytarabine[30], which was administered in 2 of the 4 reported cases[3,current report], (fourth patient received unspecified chemotherapy[1]). Aspergillus then invades the appendiceal wall due to immunosuppression from (2) neutropenia and (3) acute leukemia[31]. The patients, despite immunosuppression, still present clinically (4) with RLQ pain and fever suggestive of appendicitis; and (5) the patients with Aspergillus infection should not respond to conventional antibacterial or anti-Candidial antibiotics.

Patients satisfying this pentad should be: (1) evaluated for Aspergillus by microscopic examination with special stains, such as Grocott-Gomori methenamine silver or periodic acid-Schiff (PAS)-diastase stains, supplemented by immunohistochemistry as necessary because the fungal elements may not be readily visible on routine hematoxylin and eosin stained slides; (2) should have the entire resected appendix submitted for histologic examination if the standardly reviewed one or two representative sections of the appendix lack identifiable fungal structures; and (3) should be considered for empiric anti-Aspergillus therapy if doing poorly on conventional antibiotic therapy pending a tissue diagnosis. The importance of early anti-Aspergillus therapy is emphasized by two of the four reported cases of isolated Aspergillus appendicitis improving dramatically after instituting anti-Aspergillus therapy and appendectomy. Of note, the prognosis of isolated Aspergillus appendicitis appears to be better than that of Aspergillus appendicitis combined with Aspergillus enterocolitis.

This work illustrates that neutropenia after chemotherapy is an important risk factor for Aspergillus appendicitis/enterocolitis, and emphasizes the importance of filgrastim therapy to decrease the severity or duration of neutropenia after chemotherapy. Filgrastim helps prevent febrile neutropenia from Aspergillus or other opportunistic infections in experiments in mice[32,33], or in clinical trials[34,35], and is likely important in treating Aspergillus appendicitis or enterocolitis occurring in the setting of neutropenia.

The proposed pentad is subject to criticism. First, the data are limited to four cases of isolated Aspergillus appendicitis and four cases of Aspergillus appendicitis with other GI involvement, and therefore require further confirmation. However, all four case reports generally satisfied the proposed pentad. Second, the reviewed cases may lack clinical details because of their retrospective nature. Third, cases obtained from the literature, particularly individual case reports, are subject to reporting bias. For example, clinicians might selectively report and journal editors might selectively publish only dramatic cases of poor response to antibacterial therapy and rapid recovery after instituting anti-Aspergillus therapy. Fourth, although the proposed syndromic pentad may be highly sensitive for Aspergillus appendicitis, the specificity is unstudied and might only be moderate. The differential diagnosis in patients satisfying this pentad also includes (bacterial) neutropenic typhlitis, with or without bacterial appendicitis[36,37], and appendicitis caused by other fungi[38], including Candida[29], Mucor[39], and Histoplasma[40,41]. Therefore, this pentad should not be viewed as diagnostic, but merely as clinically useful to raise a suspicion of potential Aspergillus appendicitis. All five criteria appear to be typical for Aspergillus appendicitis, but the first four criteria may also occur with (bacterial) neutropenic typhlitis/enterocolitis and only the fifth criterion of poor response to conventional therapy is relatively specific for Aspergillus appendicitis.

This clinical pentad may become increasingly important clinically because of an increasing incidence of invasive Aspergillus[42], and an increasing incidence of severe neutropenia from more potent immunosuppressive chemotherapy and more frequent stem cell transplantation[14]. It is important to recognize neutropenic patients with invasive Aspergillus because they may fare poorly with solely antibacterial or anti-Candidial therapy (*e.g.,* fluconazole) without specific anti-Aspergillus therapy (*e.g.,* voriconazole or amphotericin). Addition of another factor to the pentad of persistently positive galactomannan antigenemia in patients with suspected appendicitis might be useful diagnostically but is not warranted at this point because of a lack of data in the reported cases of appendiceal aspergillosis[43].

**Comments**

***Case characteristics***

An 8-year-old boy with acute myelogenous leukemia, diagnosed one month earlier, and with profound neutropenia, after receiving two cycles of IV chemotherapy with daunorubicin, cytarabine, thioguanine, etoposide and dexamethasone, presented with low-grade pyrexia and chills for one day.

***Clinical diagnosis***

Physical examination revealed temperature = 36.8 0C, pulse = 111 beats/min, blood pressure = 94/63 mmHg. and mild right lower quadrant (RLQ) tenderness without rebound tenderness. The leukocyte count=200 cells/mm3 (normal 4800-10100 cells/mm3), neutrophil count < 100 cells/mm3 (normal 1600-7200 cells/mm3), hematocrit = 36.3% (normal in male boy, age 6-9 years: 33.6%-43.4%), and platelet count = 90000/mm3 (normal 150000-400000/mm3).

***Differential diagnosis***

Clinical presentation is an episode of febrile neutropenia. The differential diagnosis includes neutropenic typhlitis and/or appendicitis, due to local opportunistic infections including bacterial infections, Candida, Mucor, Histoplasma, or Aspergillus.

***Laboratory diagnosis***

The leukocyte count = 200 cells/mm3 (normal 4800-10100 cells/mm3), and neutrophil count < 100 cells/mm3 (normal 1600-7200 cells/mm3). These findings demonstrate profound neutropenia.

***Imaging diagnosis***

Abdomino-pelvic computed tomography scan revealed a dilated appendiceal lumen, thickened appendiceal wall, and periappendiceal fat stranding, findings consistent with appendicitis.

***Pathological diagnosis***

Microscopic examination of hematoxylin and eosin stains of histologic sections of the resected appendix showed an acute necrotizing appendicitis, with scattered questionable fungal hyphal forms. A Grocott-Gomori methenamine-silver nitrate stain performed on the resected specimen revealed numerous fungal hyphae that showed features characteristic of Aspergillus of septation and acutely angled branching, and which was confirmed as Aspergillus by immunohistochemistry.

***Treatment***

The patient underwent appendectomy for the appendicitis and was administered IV filgrastim (granulocyte colony stimulating factor) for the profound neutropenia. On postoperative day 13 IV amphotericin-B therapy was added when Aspergillus appendicitis was identified by special stains performed on the resected appendix.

***Related reports***

Review of the modern literature revealed only 3 other reported cases of isolated Aspergillus appendicitis, aside from one case very briefly reported in German in 1959.

***Experiences and lessons***

Analysis of the current case and review of the three prior case reported in the modern literature, suggest that patients with Aspergillus appendicitis may clinically present with a pentad of: clinically-suspected appendicitis, neutropenia, recent chemotherapy, acute leukemia, and poor clinical response if treated solely by antibacterial/anti-candidial therapy.

***Peer-review***

The strengths of the article include: reporting a well-documented case of isolated Aspergillus appendicitis, thorough review of the three previously reported cases as identified by review of the modern literature, and the proposal of a clinical pentad to facilitate clinical recognition of Aspergillus appendicitis. The main weakness, as pointed out by peer review, is that only four cases have been reported of isolated Aspergillus appendicitis, and therefore the conclusions about the general clinical presentation of this infection are tentative and require further confirmation.

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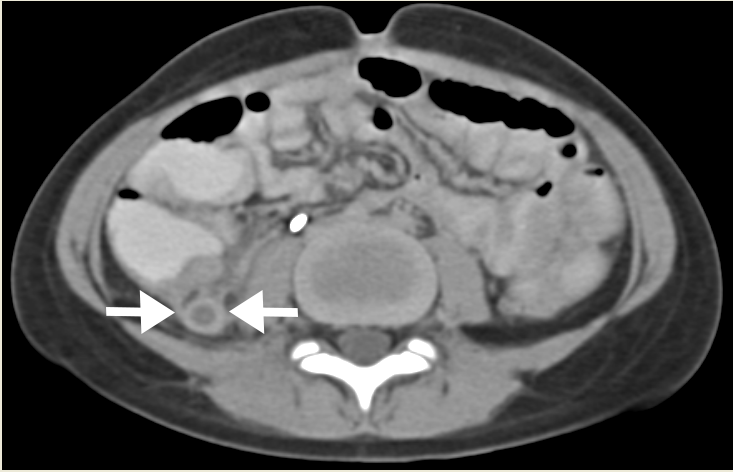
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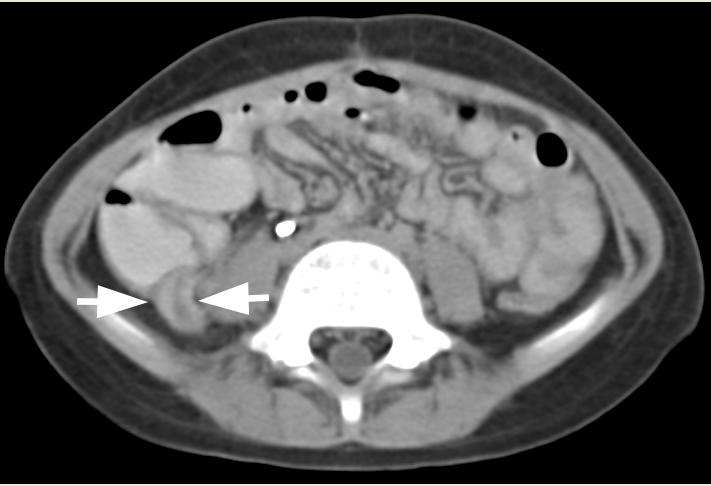
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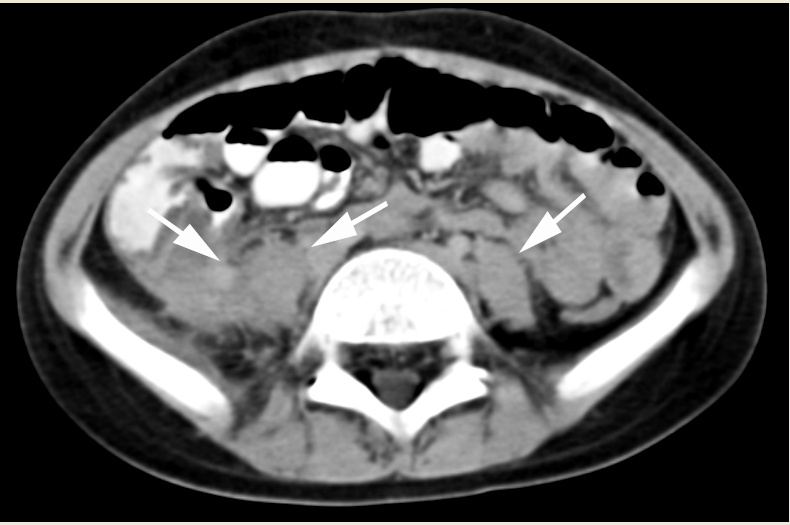
A



B



C



D

**Figure 1 computed tomography images.** computed tomography images of abdomen using IV non-ionic contrast and standard oral contrast demonstrates dilated appendiceal ostium and thickened appendiceal wall in cross-section (arrows in A); dilated lumen and thickened wall of vermiform appendix in longitudinal section (arrows in B); periappendiceal fat stranding (arrows in C, A = appendix in C); and an enlarged right psoas muscle with indistinct margins from local extension of the appendiceal inflammation (enlarged right psoas muscle with indistinct margins identified in D by 2 arrows, as compared to normal-sized left psoas muscle with distinct margins identified by 1 arrow). The appendix measures approximately 11 mm in diameter from outer wall to outer wall. All these findings are consistent with acute appendicitis. There is no evident appendicolith or typhlitis.

C:\Users\dr2364\Desktop\Aspergillusappendicitisfolder\ASPERGILLUS-FINAL-FIGURE-2A-H&E.tif

C:\Users\dr2364\Desktop\Aspergillusappendicitisfolder\ASPERGILLUS-FINAL-FIGURE-2B.tifA

B

**Figure 2 Photomicrograph.** A: Photomicrograph of a hematoxylin-eosin stained, full thickness, cross-section of the resected appendiceal specimen shows a thickened appendiceal wall due to a severe mixed inflammatory infiltrate (A, low power). The high power view (A-inset) of the area, indicated by an asterisk on the low power view, shows one questionable fungal hyphae (arrowhead) within a gland partially destroyed by the necrotizing inflammation (arrow); B: Photomicrograph of a Grocott-Gomori methenamine-silver (GMS) nitrate stain reveals invasive, septate, hyphal forms with acutely angled branches, characteristic of Aspergilus species (B-right side-low power, B-left lower inset-high power). The hyphae are confirmed as Aspergillus species by immunohistochemistry (B-left upper inset-high power).

**Table 1 Case reports of isolated Aspergillus appendicitis without other known Aspergillus infection**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Age and sex (reference)** | **Underly-ing condition** | **Chemotherapy received prior to appendicitis** | **Symptom appearance after initiating chemotherapy** | **Neutro-penia at presen- tation** | **Abdominal imaging** | **Pathologic findings in resected appendix** | **Therapy and outcome** |
| 8-yr-old male[1] | ALL | Initial therapy: Vincristine, prednisolone, L-asparaginase, intra- thecal methotrexate.  Chemotherapy during relapse not reported. | 14 months after therapy restarted for a relapse. | Yes. | USD: enlarged appendix, cecal wall thickened, and small periappendiceal fluid collection. | Necrosis and inflammation in mucosa and nearby muscle consistent with acute appendicitis. Many septated fungal hyphae showing acute-angle branching, characteristic of Aspergillus. | Fared poorly for 10 d while treated with conventional antibiotic therapy of ceftazdime and amikacin before undergoing appendectomy. Did well after appendectomy. Discharged in stable condition at postoperative day 10 (not mentioned whether received antifungal therapy after appendectomy). |
| 41-yr-old male[2] | ALL- (B-cell type with BCR-ABL trans-location). | Induction therapy: cyclophosphamide, daunorubicin, vin-cristine, prednisone, L-asparaginase, and dasatinib; Maintenance therapy: 6-mercaptopurine and dasatinib; Received stem cell transplantation. | 12 d after transplantation; 5 mo after initiation of chemotherapy. | Yes. | CT: cecal wall thickened, thickened retrocecal appendix, and periappendiceal inflammatory changes; small amount of free fluid present. | Full-thickness invasion of appendiceal wall including serosa; fungal angioinvasion with vessels occluded by hyphal forms; positive methenamine-silver stain. | Fared extremely poorly for 6 d with conventional antibiotic therapy plus acyclovir and fluconazole. Improved after appendectomy and after receiving liposomal amphotericin B and micafungin (switched on day 3 to voriconazole and micafungin due to acute renal injury). Discharged 46 d after appendectomy. Clinically stable 12 mo after hospitalization, without further aspergillus complications. |
| 21-yr-old male[3] | AML- M1. | Mitozantrone and cytarabine.  Later treatment with daunorubicin and cytarabine. | 30 d after diagnosis. | Yes. WBC = 500/mm3 (no neu- trophils seen) | USD: dilated bowel loops and right hydronephrosis.  CT scan: right hydroureter extending down into pelvis with loss of fat planes in the region, consistent with inflammatory process around distal ureter. | Coagulative necrosis of appendiceal tip with septate fungal hyphae with dichotomous branching pattern, permeating and occluding arterial branches.  Immunoperoxidase stain demonstrated Aspergillus flavus. | Amphotericin B  Second laparotomy 6 d after first showed 3 small bowel perforations.  Died at day 49 from bleeding from Aspergillus invasion of iliac vein. |
| 39-yr-old, sex not stated[6]1 | Not reported. | NA | NA | Not reported. | Not reported (case published in 1959 before abdominal CT or USD became available). | At surgery: inflamed, enlarged, gangrenous appendix with severe surrounding inflammation. Microscopic pathology not reported. | Did poorly postoperatively with high spiking fevers, overwhelming sepsis, and progressive jaundice while receiving streptomycin and 2 other antibacterial antibiotics. On day 9 therapy with antimycotic trichomycin initiated after Aspergillus nidulans isolated from appendiceal culture. Died 3 d later from progressive organ failure. |
| 8-yr-old male  [Current Case Report] | AML-M5. | Daunorubicin, cytarabine, thioguanine, etopiside, and dexamethasone. | 30 d. | Yes. WBC=  200/mm3 | USD: no evident right lower quadrant abscess or free fluid. CT: inflammatory changes in right lower quadrant with thick-walled appendix and dilated appendiceal lumen. | Branched, septate fungal hyphae invading full thickness of appendiceal wall without discrete perforation. | Underwent appendectomy: Did poorly initially postoperatively while receiving antibacterial antibiotics. Recovered after receiving amphotericin B and discharged after 21 d of this therapy.  No signs of disseminated Aspergillosis during 8 mo of follow up while receiving prophyliaxis with itraconazole. |

1Case excluded from analysis in this paper because this case report was published in 1959 before modern imaging tests became available and this case report lacks critical clinical details due to its brevity. AML: Acute myelogenous leukemia; ALL: Acute lymphocytic leukemia; CT: Computerized tomography; USD: Ultrasound; DIC: Disseminated intravascular coagulation; WBC: White blood cell; NA: Not available.

**Table 2 Reported cases of Aspergillus appendicitis with additional gastrointestinal involvement**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Age and sex. areas of aspergillus infection [reference]** | **Underly-ing condition** | **Chemotherapy received prior to appendicitis** | **Presentation with symptoms after initiation of chemotherapy** | **Neutropenia at time of developing symptoms** | **Abdominal imaging** | **Pathologic findings in resected appendix** | **Antifungal therapy:**  **Outcome** |
| 11-yr-old male.  Extensive GI involvement including appendix and cecum (typhlitis)  [28] | AML | Cytarabine, daunorubicin, and etoposide. | Day 12 after initiating chemotherapy. | Yes | USD: thickened intestinal walls with indistinct hypoechogenic area reaching from cecal pole to mesenteric root. | Performed cecal resection and appendectomy. Chronic, partially hemorrhagic inflammation of intestine infiltrated by Aspergillus. Fungal hyphae also demonstrated within blood vessels. | Amphotericin B and fluoro-cytosine: Patient succumbed to septic shock while on persistent antifungal therapy 6 wk after admission. Autopsy demonstrated disseminated Aspergillosis. |
| 38-yr-old male. Only appendix and cecum infected[26] | ALL | Vincristine and prednisone and intrathecal methotrexate. Later changed to cytoxan and Adriamycin. | Hospital day 7. | Yes, WBC = 100/mm3 | Gallium scan: increased uptake in midabdomen and pelvis consistent with infectious process.  CT: increased density in right lower quadrant consistent with an abscess or fluid-filled cecum. | Laparotomy: appendix not found (apparently due to destruction), but cecal perforation with surrounding abscess with multiple coloenteric fistulas found. Resected specimen showed Aspergillus hyphae in necrotic area of bowel wall invading peritoneal surfaces. | Amphotericin B: Stable at 6 mo follow-up, with right lung infiltrate that identified on previous x-ray, being stable in size. |
| 62-yr-old female.  Appendix, cecum, ascending colon and ileum infected[27] | AML M6 | Induction therapy: cytarabine for 7 d and idarubicin for 3 d. | Day 16 after initiating chemotherapy. | Yes, WBC = 600/mm3, no neutrophils. | CT: inflammatory changes and fat stranding surrounding dilated appendix. Small amount of adjacent free fluid in pelvis. | Resected 2.5 cm segment of small bowel and 60 cm segment of cecum and ascending colon. Microscopic evaluation of sections of bowel and appendix showed transmural intestinal infarction with hemorrhagic plugs within intestine blood vessels and fungal hyphae with septation and acute branching angles. Fungal stain revealed morphology consistent with Aspergillus. | Voriconazole started empirically 20 d after admission, before surgery: Patient expired from cardiac arrest 26 d after admission. |
| 5-yr-old female. Appendix involved with widespread GI infection[29] | AML and diffuse large B-cell lymphoma | 6 cycles of ThaiPOG protocol. | Not specified. | Yes. | CT: early abscess formation in distal ileum and appendix. | Pathological confirmation of appendicitis caused by invasive aspergillosis. | Amphotericin B, metronidazole and piperacillin with tazobactam: Died 1 d later from septicemia with DIC; Autopsy disclosed fungal infection disseminated throughout body. |

GI: Gastrointestinal; AML: Acute myelogenous leukemia; ALL: Acute lymphocytic leukemia; NA: Not applicable; WBC: White blood cell; CT: Computerized tomography; USD: Ultrasound; DIC: Disseminated intravascular coagulation.

Figure 2A