DOI: 10.4274/terh.galenos.2021.70846
J Tepecik Educ Res Hosp 2022;32(3):481-7

CASE REPORT / OLGU SUNUMU

Invasive Aspergillosis of the Small Bowel in a Patient with Acute Lymphoblastic Leukemia: Case Report and a Systematic Review of the Literature

Akut Lenfoblastik Lösemili Bir Hastada İnce Bağırsağın İnvazif Aspergillozisi: Olgu Sunumu ve Literatür İncelemesi

Nilgün Eroğlu[1], Ayşenur Bahadır[1], Erol Erduran[1], Gülay Kaya[2], Hatice Sonay Yalçın Cömert[3], İsmail Saygın[4], Zeynep Gökçe Gayretli Aydın[5]

[1]Karadeniz Technical University Faculty of Medicine, Department of Pediatric Hematology and Oncology, Trabzon, Turkey
[2]Karadeniz Technical University Faculty of Medicine, Department of Pediatric Care Unit, Trabzon, Turkey
[3]Karadeniz Technical University Faculty of Medicine, Department of Pediatric Surgery, Trabzon, Turkey
[4]Karadeniz Technical University Faculty of Medicine, Department of Pathology, Trabzon, Turkey
[5]Karadeniz Technical University Faculty of Medicine, Department of Pediatric Infection Disease, Trabzon, Turkey

Cite as: Eroğlu N, Bahadır A, Erduran E, Kaya G, Yalçın Cömert HS, Saygın İ, Gayretli Aydın ZG. Invasive Aspergillosis of the Small Bowel in a Patient with Acute Lymphoblastic Leukemia: Case Report and a Systematic Review of the Literature. J Tepecik Educ Res Hosp 2022;32(3):481-7

Abstract

In invasive aspergillosis (IA), which is among the opportunistic infections in immunocompromised individuals, high rates of morbidity and mortality can be observed. This disease is most commonly seen in the respiratory tract, but has also been reported in the sinuses, central nervous system, skin, liver, and urinary tract. Aspergillosis, which can be seen outside the lung, is usually seen in disseminated disease. Although aspergillosis, which can be seen in the gastrointestinal tract, is the least common form, it may progress with complications in the follow-up. We present a patient who was followed up with the diagnosis acute leukemia and developed small bowel ileus due to IA after pulmonary aspergillosis while chemotherapy was continuing. We presented our case in a literature review. Pulmonary aspergillosis due to aspergillus was detected in a 3-year-old patient, who was diagnosed with acute lymphoblastic leukemia and relapsed while chemotherapy was continuing. The patient, who was started antifungal due to pulmonary aspergillosis, developed complaints of fever and vomiting in the follow-up. Physical examination revealed distension, defense, and tenderness in the abdominal examination. In the patient who underwent laparotomy, multiple necrotic segments were detected in the terminal jejunum and proximal ileum during the operation. Pathologically, aspergillus was detected in the resected area. Voriconazole and caspofungin were added to the patient who underwent ileum resection, but the patient died. At the time of the literature search, 12 articles on intestinal aspergillus were found. Gastrointestinal manifestations of aspergillosis may not be very specific, except for abdominal pain. If the patient has a prolonged neutropenic period, acute abdomen, gastrointestinal aspergillosis should be kept in mind even if there is no pulmonary involvement. Antifungal treatment should be started in the early period and surgical intervention should be considered in the early period for patients with acute abdomen and ileus. Dual therapy in antifungal therapy, such as combination therapy with caspofungin and voriconazole, is controversial.

Keywords: Invasive aspergillosis, small bowel, acute lymphoblastic leukemia

Address for Correspondence/Yazışma Adresi: Nilgün Eroğlu MD, Karadeniz Technical University Faculty of Medicine, Department of Pediatric Hematology and Oncology, Trabzon, Turkey
Phone: +90 505 737 27 11 **E-mail:** dr-nilguner@hotmail.com
ORCID ID: orcid.org/0000-0002-9956-4054

Received/Geliş tarihi: 11.08.2020
Accepted/Kabul tarihi: 17.03.2021

Öz

Genellikle immün yetmezliği olan konakçılarda fırsatçı bir enfeksiyon olarak görülen invaziv aspergilloz (IA), yüksek morbidite ve mortalite ile ilişkilidir. IA, izole olarak solunum sisteminde, nazal sinüslerde, merkezi sinir sisteminde, deride, karaciğerde ve idrar yollarında ortaya çıkar. Extrapulmoner aspergilloz ise genellikle dissemine olarak görülür. Gastrointestinal aspergillozis, IA'nın en az görülen şekli olmasına rağmen ciddi sonuçlara neden olabilir. Bu yazıda, kemoterapi alan ve pulmoner aspergilloz gelişen akut lösemili bir hastada IA'ya bağlı ince bağırsak ileus olgusunu sunduk. Literatürün de sistematik bir incelemesini yaptık. Kemoterapi altında dirençli ve nüks akut lenfoblastik lösemili 3 yaşında bir kız çocuğunda kemoterapiye bağlı şiddetli nötropeni ve pulmoner aspergilloz gelişti. Hasta, ateş ve kusma ile başvurdu. Muayenede soluk görünümde ve batın aşırı derecede distandü, hassas idi. Laparotomi sırasında terminal jejunum ve proksimal ileumda çoklu nekrotik segment saptandı. Aspergillus nekrotik segmentten izole edildi. İleum rezeksiyonu yapıldı. Hastaya vorikonazol ve kaspofungin uygulanmasına rağmen hasta kaybedildi. Literatür derlemesinden bağırsak IA ile ilgili daha önce tek olgu raporlarında veya küçük olgu serilerinde yayınlanmış 12 makale incelendi. Gastrointestinal aspergillozda klinik belirtiler genellikle karın ağrısı gibi non-spesifiktir ve nadiren akut batın görülür. Akciğer tutulumu olan veya olmayan şiddetli ve uzun süreli nötropenik hastalarda doğru tedavi ve acil cerrahi uygulanabilmesi açısından gastrointestinal aspergillozdan şüphelenilmelidir. Bu yazıda, erken cerrahi müdahalenin ve kombine antifungal tedavinin önemini vurgulanmaktadır. Bununla birlikte, antifungal ajanlarla kombinasyon tedavisi, özellikle kaspofungin ve vorikonazol ile kombinasyon tedavisi ile ilgili verilerin tartışmalı olduğu ve prospektif çalışmalara ihtiyaç olduğu vurgulanmalıdır.

Anahtar Kelimeler: İnvaziv aspergillus, ince bağırsak, akut lenfoblastik lösemi

Introduction

Aspergillus is a factor in the saprophytic spore-producing fungi group and is very common in our environment[1]. The mode of transmission of the disease to humans is by inhalation of airborne conidia. In people who are not sick, spores are tried removed by mucociliary clearance, but in cases where they cannot be removed, a proinflammatory response occurs with phagocytosis of alveolar macrophages and the spores are cleared[2]. Those that cannot be eliminated are also killed by neutrophils. Spores escaping from the host defense, on the other hand, invade the endothelial cells of the vascular structures through the circulation and spread to the organs. If there is a deficiency in the host immune system, the risk of invasive aspergillosis (IA) increases. Therefore, the risk increases in patients with malignancy who remain neutropenic for a long time and receive chemotherapy[2].

Primary IA of the small bowel is rare and associated with high mortality. We report a patient with acute lymphoblastic leukemia (ALL) who developed isolated IA of the small bowel with the literature. The girl was treated with early surgery and combination antifungal therapy but finally she died.

Materials and Methods

We present a patient with ALL who developed multiple small bowel necrosis while receiving chemotherapy. The literature was searched using the Pubmed database. During scanning, the words "intestinal aspergillosis", "gastrointestinal system (GIS) aspergillosis", "extra-pulmonary aspergillosis" and "digestive system aspergillosis" were used. The patient informed consent form was obtained.

Results

Case Report

3.5 years old female patient; was diagnosed high-risk T-cell ALL and St. Jude Total XV chemotherapy protocol was started. She developed central nervous system (CNS) relapse after high dose methotrexate treatment of consolidation block. Reintensification treatment was applied and after the second intratechal treatment, cerebrospinal fluid (CSF) cytology was negative. Two months later, she developed second CNS relapse, second reintensification treatment and 16 days 24 Gy craniospinal radiotherapy was applied. Ten days after the end of radiotherapy with 175,000/µL white blood cell count, bone marrow relapse was determined and ALL-R17 chemotherapy protocol was initiated. Concomitant intrathecal treatment was applied, CSF protein was 50 mg/dL and cytology was reported as benign. In ALL-R17 A block therapy; vincristine 1.5 mg/m^2, etoposide 25 mg/m^2, ARA-C 25 mg/m^2, dexamethasone 6 mg/m^2 were applied. In the bone marrow aspiration (BMA) which was made at the end of the ALL-R17 block 4% blast was detected. Five days later after the A block therapy treatment with piperacillin-tazobactam was initiated with the cause of neutropenic fever in the follow-up when planned to continue to block B. Liposomal amphotericin B 1 mg/kg and trimethoprim sulfamethoxazole 5 mg/kg prophylactically continued. Continuation of the resistant fever on the 6th day of neutropenic fever upon the presence of streptococcus mitis in the catheter culture, gradually therapy progressed with meropenem, vancomycin, amikacin and metronidazole. At the follow-up period, 25 days of neutropenia, the galactomannan antigen level

was elevated 4.6, and the liposomal amphotericin B was increased to 5 mg/kg. In follow-up; she developed abdominal distension, bilious vomiting and dilation in transverse colon, 5 mm wall thickness was determined by abdominal ultrasound (USG). Abdominal computed tomography (CT) showed an appearance consistent with the ileus. On chest CT, soft tissue densities of nodules were detected in the upper lobes of both lungs (pneumocystis carini pneumonia, viral pneumonia?). In the right upper lobe posterior segment of the right lung and in the lateral segment of the middle lobe 2x5 mm in size. Trimethoprim/sulphomethoxazole was increased to 20 mg/kg treatment dose. Echocardiography and cranial magnetic resonance imaging were evaluated as normal for the detection of systemic fungal infection. On day 2 of liposomal amphotericin B treatment, total/direct bilirubin value was elevated to 8.83/5.83 and amphotericin B was replaced by voriconazole. Abdominal distension wasn't regressed, and she was operated with laparotomy. Necrotic areas and brit were found in the small intestine and the colon, and a 50 cm segment of the jejunum was resected (Figure 1, 2). The patient was followed up on an intensive care unit after the operation, and extubated on the 6th day. The abdominal drain was withdrawn on the 20th day. When macroscopically irregular transmural necrosis and necrotic areas were detected, aspergillus infection was detected. In the hypha structure, which showed 45 degrees of angulation in the submucosal areas of intestinal vascular structures in pathology (Figure 3, 4). Galactomannan antigen level was determined 3.5 on the 19th day of voriconazole treatment and caspofungin was added to the treatment (loading dose 70 mg/m^2 on day 1, followed by 50 mg/m^2 daily). On the 23th day of intensive care follow-up, right central fascial paralysis was developed, and intrathecal treatment was applied for the third time relapse of CNS relapse. CSF protein level was 118 mg/dL and cytology was malignant.

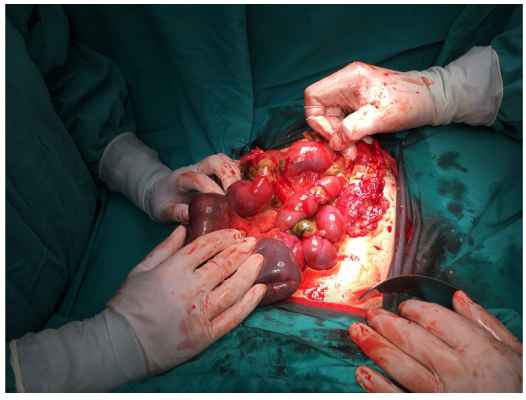

Figure 1. Multiple small bowel ulcerations revealed during emergency laparotomy

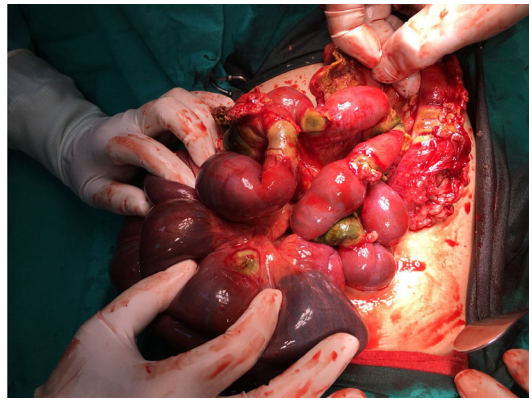

Figure 2. Multiple small bowel ulcerations, necrosis revealed during emergency laparotomy

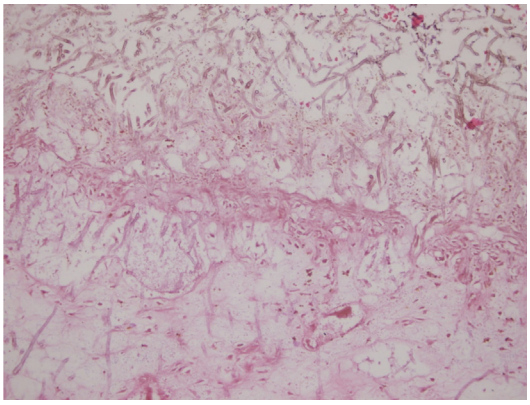

Figure 3. Hematoxylin and eosin-stained histological section showing aspergillus septate hypha branching at 45-degree angle HE x200

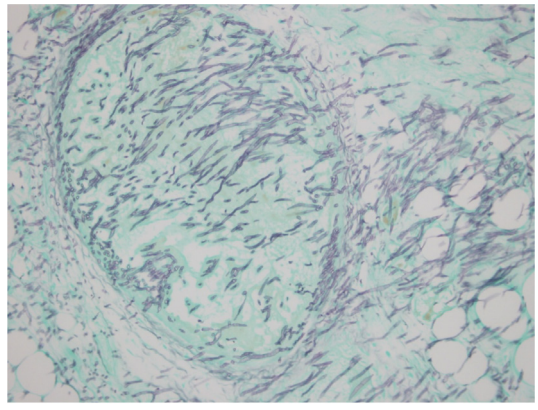

Figure 4. Grocott's methenamine silver stain, original magnification x200

Table 1. General characteristics of pediatric patients with primary gastrointestinal aspergillosis

Article	Number of cases	Age/ years	Underlying disease	Previous infection	Chemoteraphy	Neutropenia at diagnosis
Fischer et al.[3]	5	3-16	ALL	No	AIEOP-BFM ALL 2000	Yes
Decembrino et al.[4]	1	6	AML	No	AIEOP AML 2002/01	Yes
Florescu et al.[5]	4	-	Posttransplant	Small Bowel Transplantation	High-dose steroids OKT3 monoclonal antibody	Yes
Lehrnbecher et al.[6]	1	10	PNET	Yes	Thiotepa carboplatin etoposide	Yes
Ibrahim et al.[7]	1	1,5	Abdominal lymphoma	No	?	No
Marterre et al.[8]	1	9	ALL	No	Vincristine prednisone	Yes
Avcu et al.[9]	1	5	ALL	Yes	ALL BFM 2000	Yes
Reyna-Figueroa et al.[10]	1	13	ALL	No	Larson regimen	Yes
Karaman et al.[11]	1	10	Arthrogryposis multiplex congenita	No	None	No
Franciosi et al.[12]	1	2,5	DiGeorge's syndrome (isolated T-cell immunodeficiency)	Yes	None	No
Kayiran et al.[13]	2	6 and 4 months	Combined immunodeficiency and transient hypogammaglobulinemia of infancy	No	No	No
Hayden et al.[14]	1	1	AML	No	MRC AML12	Yes

GIS: Gastrointestinal system

Clinical presantion	Secondary dissemination	Portion of GIS tract involved	Antifungal prophilaxy	Antifungal theraphy (pre-emptive)	Antifungal theraphy (finally)	Outcome at 28 days
Constipation, upper GIS bleeding, distended abdomen, abdominal pain	Yes (n=1)	Proximal jejunum, colon, apendix vermiformis	Cotrimoxazole (n=3) Fluconazole (n=2) Oral amphotericin B (n=2)	Caspofungin (n=1) Fluconazole (n=2) Itraconazole (n=1)	Voriconazole (n=2) Liposomal amphotericin B (n=3) Caspofungin (n=2) Itraconazole (n=1)	Survived (n=1) Died (n=4)
Distended abdomen, abdominal pain	No	Apendix vermiformis	Flucanozole	Liposomal amphotericin B	Voriconazole	Survived
Distended abdomen, abdominal pain	Yes	Small bowel	Flucanozole oral amphotericin B	Echinocandins (micafungin or caspofungin) voriconazole	Fluconazole echinocandin voriconazole amphotericin B	Survived
Vomiting, abdominal pain, diarrhea	No	Terminal jejunum, proximal ileum	Fluconazole oral amphotericin B	Liposomal amphotericin b voriconazole	Voriconazole	Survived
Abdominal masses	No	Small bowel	-	Liposomal amphotericin B	-	Died
Distended abdomen, abdominal pain	No	Small bowel	-	Liposomal amphotericin B	-	Survived
Gastrointestinal bleeding abdominal distension jaundice	Yes	Small bowel	-	Caspofungin voriconazole liposomal amphotericin B posaconazole	Posaconazole	Survived
Abdominal pain, constipation, distended abdomen	No	Small bowel	Fluconazole	Caspofungin	-	Died
Abdominal pain, abdominal swelling vomiting	No	Colon	-	Surgery	-	Survived
Melena, peritonitis	No	Small bowel	-	?	-	Survived
Vomiting	No	Duedonum	-	Liposomal amphotericin B	-	Survived
Distended abdomen	Yes	Terminal ileum	-	Liposomal amphotericin B itraconazole voriconazole	Voriconazole	Survived

Treatment was switched to the ALL-Rez BFM 2002 protocol. After the F1 and F2 blocks, galactomannan level was 2.9. In the control abdominal CT, diffuse wall thickening was detected and Jejunal intestine was measured 4 mm; in thorax CT, newly emerging solid nodules were observed in the right lung upper lobe posterior and middle lobe lateral segment, and the left lung lower lobe superior segment in the largest 9x8 mm size, and the findings were evaluated as compatible with IA. After F2 block treatment, BMA was performed and bone marrow relapse was accepted. Fludarabine, cytarabine, granulocyte colony-stimulating factor (G-CSF), and idarubicin (FLAG-IDA) treatment was initiated. After 1 week of the FLAG-IDA, on the day of varicosanol treatment 81, and 63 of caspofungin her overall situation has deteriorated. She developed ileus again and subsequently died.

Review of the Literature

When the literature was reviewed, it was observed that most of the publications on GIS aspergillosis consisted of case series. There are 12 articles and 20 pediatric aspergillosis cases in the literature[3-14]. The mean age is 5.4 years (range 1 month-16 years). Underlying disease acute leukemia in 10 patients (ALL: n=8, acute myeloid leukemias: n=2), lymphoma in 1 patient, CNS primitive neuroectodermal tumor in 1 patient; in the remaining cases, non-haematological diseases (Di George's syndrome, arthrogryposis multiplex congenita, combined immune deficiency). Fifteen patients (75%) were neutropenic at the time of diagnosis. Sixteen patients recently received a course of chemotherapy. The clinical presentations included diarrhea in 1 patient, constipation in 3 patients, vomiting in 2 patients, abdominal pain in 7 patients, abdominal bloating in 8 patients, GIS bleeding in 3 patients, abdominal mass in 1 patient, and jaundice in 2 patients. Abdominal imaging (radiography, ultrasonography, CT) was applied to 16 cases: 2 of the 5 abdominal USG findings were normal and endoscopic was examined. Abdominal CT revealed GIS abnormalities (isolated or widespread edema and thickening of the intestinal wall) in 5 cases, all other cases were evaluated with abdominal X-ray. Seven cases were disseminated, the other 13 cases had GIS lesions (Table 1).

Discussion

In this study, an ALL patient with gastrointestinal aspergillus infection was presented. New antifungal agents have been useful for treating aspergillosis over the last few years [9,15-17]. Increased use of voriconazole for treatment and antifungal prophylaxis for neutropenic leukemia patients decreases the mortality due to fungal infection. In this study; despite the use of liposomal amphotericin B, small bowel, and colon aspergillus infection was developed.

GIS aspergillosis is the most common site of IA, and the small intestine is mostly involved in the gastrointestinal tract[9,18,19]. Additionally, although angioinvasive and bronchoalveolar respiratory system involvement is common, other system involvement such as the CNS, cardiovascular system, joints, eyes and skin have also been reported[19]. In the gastrointestinal tract of aspergillus infection, intestinal perforation can be seen with infarct tissue ischemia after vascular thrombosis[9]. Necrotic tissues may develop in IA after ischemia[20-22]. Among the clinical findings, abdominal pain, diarrhea, bleeding can be seen, and rarely, acute abdomen may develop due to obstruction and perforation in the small intestines[23].

Neutropenia is one of the most important risk factors for developing fungal infection, particularly aspergillosis, in malignant diseases undergoing chemotherapy[24]. However, in the literature, the rate of neutropenia in IA cases is 1/3. One of the most important reasons is the use of immunosuppressive drugs[15,25]. The risk increases, particularly if there is a period of neutropenia that exceeds 21 days[24]. In the literature, 60% of patients used antifungal prophylaxis, usually flucanozole and oral amphotericin B was used. In this study we were used amphotericin B for prophylaxis. In the literature, single drug (liposomal amphotericin B or caspofungin) was used for pre-emptive treatment or combined treatments were used (liposomal amphotericin, voricanozole). Finally patients were discharged from the hospital with oral voriconazole or posaconazole. In the literature, half of the patients survived, but our case died despite aggressive treatment.

Medical treatment is usually applied for the gastrointestinal involvement of aspergillosis, but surgical operation is required in cases such as obstruction, perforation, and bleeding. Surgery is also important for reducing the current fungal burden. Surgery is a good option to remove the local lesion. Karaman et al.[11], only used surgery and antifungal treatment was not recommended in this article.

The clinical and radiological findings of intestinal aspergillosis are usually nonspecific and may be confused with necrotizing enterocolitis involving the gastrointestinal tract, gastrointestinal graft-versus-host disease, and clostridium difficy enterocolitis. We excluded clostridium colitis in the differential diagnosis of our case, since there was no diarrhea and the stool test was negative.

Since the serum galactomannan level is found to be high in IA in the literature, we think that a high galactomannan level may be helpful in the diagnosis of individuals without pulmonary and paranasal aspergillosis but whose fever persists for a long time and whose immune suppression is high[26].

Conclusion

In IA cases, GIS involvement is rare and the mortality rate is high. The involvement of aspergillus infection in the internal organs should be kept in mind in patients with or without pulmonary involvement with prolonged neutropenia. It should be considered in the differential diagnosis of patients, particularly in the cases with abdominal pain and prolonged fever.

Ethics

Informed Consent: The patient informed consent form was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions

Surgical and Medical Practices: H.S.Y.C., İ.S., Concept: A.B., Desing: E.E., Data Collection or Processing: N.E., Analysis or Interpretation: G.K., Z.G.G.A., Literature Search: N.E., Writing: N.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Hadchiti MT, Abdalkader M, Rached L, Mahfoud D, Khoury G, Ghanem H. Disseminated Intra-Abdominal Aspergilloma With Abdominal Wall Invasion in a Patient With Acute Myeloid Leukemia: A Case Report. Clin Lymphoma Myeloma Leuk 2015;15 (Suppl):S94-7.
2. Dagenais TR, Keller NP. Pathogenesis of Aspergillus fumigatus in Invasive Aspergillosis. Clin Microbiol Rev 2009;22:447-65.
3. Fischer J, Simon T, Hamprecht A, et al. Surgical Implications for Diagnosis and Treatment of Intestinal Aspergillosis in Pediatric Patients with ALL. Eur J Pediatr Surg 2018;28:477-83.
4. Decembrino N, Zecca M, Tortorano AM, et al. Acute isolated appendicitis due to Aspergillus carneus in a neutropenic child with acute myeloid leukemia. New Microbiol 2016;39:65-9.
5. Florescu DF, Islam KM, Grant W, et al. Incidence and outcome of fungal infections in pediatric small bowel transplant recipients. Transpl Infect Dis 2010;12:497-504.
6. Lehrnbecher T, Becker M, Schwabe D, et al. Primary intestinal aspergillosis after high-dose chemotherapy and autologous stem cell rescue. Pediatric Infect Dis J 2006;25:465-6.
7. Ibrahim AH, Malki TA, Morad N. Primary locally infiltrative gastrointestinal aspergilloma in a non-neutropaenic child. J R Coll Surg Edinb 2000;45:335-8.
8. Marterre WF Jr, Mong AT, Pulito AR. Locally ınvasive aspergillosis of the bowel. J Pediatr Surg 1992;27:1611-3.
9. Avcu G, Karapinar DY, Yazici P, et al. Difficult diagnosis of invasive fungal infection predominantly involving the lower gastrointestinal tract in acute lymphoblastic leukaemia. Med Mycol Case Rep 2016;11:1-4.
10. Reyna-Figueroa J, Luna-Aguilar FJ, Cardoso-Yah G, Rivera-Salgado MI, Limon-Rojas AE, Galindo-Delgado P. Gastric wall perforation secondary to presumed aspergillosis in a pediatric patient with aplastic anemia: A case report. J Infect Dev Ctries 2015;9:431-4.
11. Karaman I, Karaman A, Boduroğlu EC, Erdoğan D, Tanır G. Invasive Aspergillus infection localized to the gastric wall: report of a case. Surg Today 2013;43:682-4.
12. Franciosi CM, Romano F, Caprotti R, Uggeri F. Multiple gastric perforations in an immunodepressed child. Surgery 2002;131:685-6.
13. Kayiran P, Urganci N, Cetinkaya F, Tanik C. Two children with ınvasive gastrointestinal aspergillosis. Indian Pediatr 2007;44:375-7.
14. Hayden JT, Wood KM, Pedler S, Lawson A, Skinner R. Invasıve aspergillosis of the small bowel in an infant with acute myeloid leukemia and intestinal obstruction. Pediatr Hematol Oncol 2009;26:84-91.
15. Marr KA, Carter RA, Boeckh M, Martin P, Corey L. Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. Blood 2002;100:4358-66.
16. Leventakos K, Lewis RE, Kontoyiannis DP. Fungal infections in leukemia patients: how do we prevent and treat them? Clin Infect Dis 2010;50:405-15.
17. Dragonetti G, Criscuolo M, Fianchi L, Pagano L. Invasive aspergillosis in acute myeloid leukemia: Are we making progress in reducing mortality? Med Mycol 2017;55:82-6.
18. Chaudhary A, Jain V, Dwivedi RS, Misra S. Invasive aspergillosis causing small bowel infarction in a patient of carcinoma breast undergoing chemotherapy. J Carcinog 2006;5:18.
19. Di Franco G, Tagliaferri E, Pieroni E, et al. Multiple small bowel perforations due to invasive aspergillosis in a patient with acute myeloid leukemia: case report and a systematic review of the literature. Infection 2018;46:317-24.
20. Mohite U, Kell J, Haj MA, et al. Invasive aspergillosis localised to the colon presenting as toxic megacolon. Eur J Haematol 2007;78:270-3.
21. Cohen R, Heffner JE. Bowel infarction as the initial manifestation of disseminated aspergillosis. Chest 1992;101:877-9.
22. Jayshree RS, Shafiulla M, George J, David JK, Bapsy PP, Chakrabarti A. Microscopic, cultural and molecular evidence of disseminated invasive aspergillosis involving the lungs and the gastrointestinal tract. J Med Microbiol 2006;55:961-4.
23. Kazan E, Maertens J, Herbrecht R, et al. A retrospective series of gut aspergillosis in haematology patients. Clin Microbiol Infect 2011;17:588-94.
24. Gerson SL, Talbot GH, Hurwitz S, Strom BL, Lusk EJ , Cassileth PA. Prolonged granulocytopenia: the major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. Ann Intern Med 1984;100:345-51.
25. Wald A, Leisenring W, van Burik JA, Bowden RA. Epidemiology of Aspergillus infections in a large cohort of patients undergoing bone marrow transplantation. J Infect Dis 1997;175:1459-66.
26. Nucci M, Nouér SA, Cappone D, Anaissie E. Early diagnosis of invasive pulmonary aspergillosis in hematologic patients: an opportunity to improve the outcome. Haematologica 2013;98:1657-60.