

Primary gastrointestinal aspergillosis: a case report and literature review

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SUMMARY

Invasive aspergillosis is a severe infection that generally involves the lungs. Primary gastrointestinal aspergillosis is the least common form of invasive aspergillosis. A patient aged 65 years developed a febrile neutropenic episode following an autologous stem cell transplant for plasmacytoid variant diffuse large B-cell gastric non-Hodgkin's lymphoma. He had abdominal pain on the second day of the febrile neutropenic episode and ileus occurred on the sixth day. His general condition deteriorated despite broad spectrum antibiotics and caspofungin treatment, and intestinal perforation occurred on

the nineteenth day of the febrile neutropenic episode. Pathological examination of the resected jejunum and ileum revealed mould hyphae compatible with aspergillus. The patient died due to massive gastrointestinal bleeding on the fifth post-operative day. Although a rare condition, primary gastrointestinal aspergillosis should be kept in mind while treating neutropenic patients with gastrointestinal symptoms.

Keywords: aspergillosis, gastrointestinal tract, ileum, jejunum.

INTRODUCTION

Aspergillus is a mould frequently found in nature and inhalation of infectious conidia is common [1]. Inhaled conidia can cause invasive diseases in immunosuppressed patients. Disseminated disease may develop in patients with invasive pulmonary aspergillosis (IPA) due to the ability of the fungus to invade vascular structures [2]. The most common risk factors of invasive aspergillosis (IA) are haematologic malignancies, haematopoietic stem cell transplantation (HSCT), solid organ transplantation, and long-term steroid treatment [3-5].

Although the first entry point of the infectious agent into the body is the respiratory system, it may rarely enter through the gastrointestinal system [1]. Primary gastrointestinal aspergillosis (PGA) is the least common form of IA and knowledge is limited to case reports and autopsy findings [6-25]. Here, we report a patient with PGA and review the general characteristics of cases of PGA in the literature.

CASE REPORT

A 65-year-old man developed a febrile neutropenic episode (FNE) on the third day following an autologous HSCT for plasmacytoid variant diffuse large B-cell gastric non-Hodgkin's lymphoma. He had been treated with 6 cycles of R-CHOP (rituximab-cyclophosphamide, doxorubicin, vincristine, prednisolone) and a complete response had been obtained. The autologous stem cell trans-

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plantation had been performed upon early recurrence of the disease 10 months after initial treatment. He was living in an urban area and was not working. The patient was given 2 cycles of ICE (ifosfamide, carboplatin, etoposide) protocol to provide remission before HSCT. Neutropenia occurred on the tenth day after ICE protocol and lasted 4 days. Lymphopenia occurred on the third day after ICE protocol and lasted 10 days. HSCT was performed by applying BEAM (carmustine, etoposide, cytosine arabinosid, melfalan) protocol. Neutropenia occurred on the ninth day after BEAM protocol and FNE developed at the same time. Fluconazole had been given to the patient at a dose of 200 mg once a day for prophylaxis against the yeast infection. Chest X-ray was normal and physical examination was normal other than a body temperature of 38.4°C. Biochemical examination revealed C-reactive protein (CRP) 8 mg/L (normal: 0-5) and procalcitonin 4.19 ng/mL (normal <0.5 ng/mL). Piperacillin/tazobactam was initiated empirically. A slight abdominal pain developed on the second day of treatment. There was slight tenderness in the abdomen of the patient during palpation. Abdominal ultrasonography showed fine perisplenic fluid. Abdominal computed tomography (CT) revealed an increased thickness of the jejunal wall (thickness 10 mm) (Figure 1). Thorax tomography was normal. Treatment was switched to a combination of colistin, tigecyclin and meropenem on the fourth day of FNE because carbapenem resistant *Klebsiella pneumoniae* was isolated from blood cultures. Procalcitonin was 5.11 ng/mL, and serum CRP level was 366 mg/L on the first day of this treatment. Ultrasonography, that was done on the sixth day of FNE because of worsened abdominal pain and new-onset vomiting, revealed a dilatation in the small intestines. Abdominal tomography showed an increased thickness of the jejunal wall (at the same size as before), dilatation of the whole small intestines except the terminal ileum, misty mesentery, and a large number of mesenteric lymphatic ganglion, the largest being 14x10 mm. Thorax tomography was normal. A nasogastric tube was inserted, and 2000 mL of gastric fluid was removed from the stomach. Neutropenia lasted 8 days. Caspofungin was added empirically due to the gradual deterioration of clinical and laboratory parameters on the eleventh day of FNE. At this time, abdominal pain was worse,

body temperature was high, serum CRP level was 405 mg/L, and serum procalcitonin level was 4.98 ng/mL. The patient's body temperature returned to normal after the third day of treatment with caspofungin, and abdominal pain continued with decreasing severity. Procalcitonin was 1.89 ng/mL and serum CRP level was 89 mg/L on the eighteenth day of FNE. An acute abdomen developed on the following day and abdominal CT revealed sub-diaphragmatic free air and fluid in the abdomen consistent with intestinal perforation. At this time, serum CRP level was 132



Figure 1 - Abdominal computerized tomography of the patient on the second day of febrile neutropenic episode [Two-pointed black arrows show the increased thickness of the jejunal wall (thickness 10 mm)].



Figure 2 - Macroscopic appearance of resected jejunum in the patient with primary gastrointestinal aspergillosis (Scale is 15 cm; A: Proximal part of the resected jejunum, B: All resected jejunum; necrotic and perforated areas are remarkable)

mg/L and procalcitonin level was 2.39 ng/mL. Two nodules, one with a dimension of 17x13 mm in the superior segment of the left lower lobe and the other with a dimension of 6 mm in the anterior segment of the right upper lobe were seen on thorax tomography. The patient was operated on, and necrotic and perforated areas were observed on the surface of the small intestine during the

operation. Twenty five cm of ileum and 100 cm of jejunum were resected and end-to-end anastomosis was carried out. Ulcers and necrosis were seen in the mucosa of the resected intestinal segments (Figure 2). The patient was admitted to the intensive care unit in the post-operative period and received mechanical ventilation. Upper gastrointestinal bleeding developed on the fifth day after

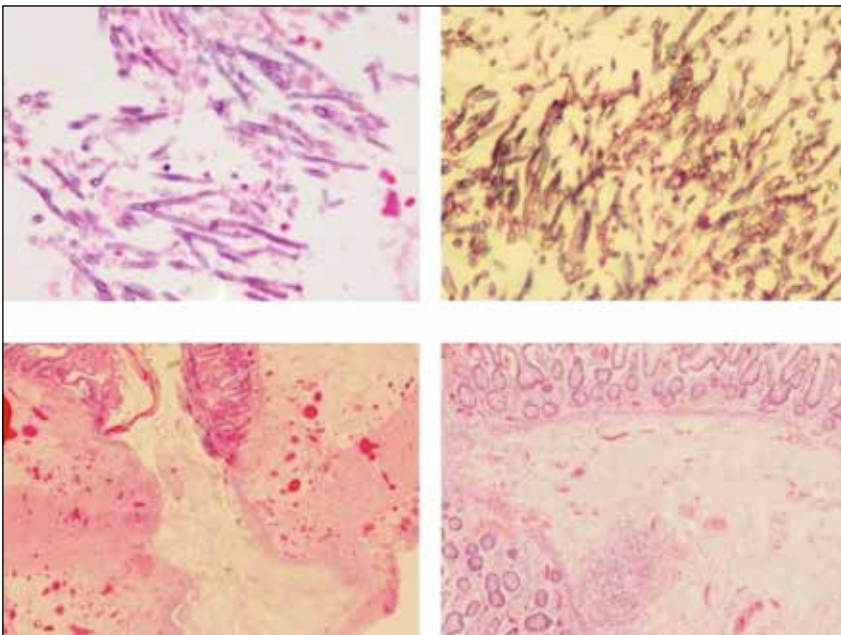


Figure 3 - Images on the pathological examination of the resected jejunum. A: Periodic acid Schiff (x400 magnification), septate mould hypha branching at 45-degree angle; B: Gomori Methenamine-Silver (x400 magnification), septate mould hypha branching at 45-degree angle; C: Hematoxylin-eosin (x20 magnification), transmural necrosis and perforation in the jejunum; D: Hematoxylin&eosin (x40 magnification), submucosal granulomatous inflammation containing giant cells

the operation. Upper gastrointestinal endoscopic examination revealed that the mucosa of the esophagus and stomach and the anastomotic line were normal. However, the mucosa of the small intestine after the anastomosis line could not be evaluated because there was too much blood in the lumen.

The patient died due to massive gastrointestinal bleeding on the fifth post-operative day. *Aspergillus* spp was isolated from the sputum culture taken the day before the death. Pathological examination of the resected intestinal segments revealed granulomas containing Langerhans-type giant cell and mould hypha branching at a 45-de-

gree angle infiltrating all intestinal layers (Figure 3). There was no angioinvasion of hypha.

■ LITERATURE REVIEW

We searched the PubMed database system using the key words (“aspergillosis”, “invasive aspergillosis”, “primary gastrointestinal aspergillosis”, “digestive tract aspergillosis”, “colonic aspergillosis”, “small bowel aspergillosis”, “jejunal aspergillosis”, “ileal aspergillosis”, “esophageal aspergillosis” and “aspergillus appendicitis”) for cases recorded between 1980 and May 2017. The refer-

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

Underlying diseases	Solid tumor, 1 (3%)	
	Hematological malignancy, 25 (78%)	Acute myeloid leukemia, 14 (56%)
		Acute lymphoblastic leukemia, 5 (20%)
		Non-hodgkin lymphoma, 4 (16%)
		Multiple myeloma, 1 (4%)
		Aplastic anemia, 1 (4%)
	Non-malignant diseases, 6 (19%)	Ulcerative colitis
		Necrotizing fasciitis
		Overlap syndrome
		Cirrhosis
Pneumococcal pneumonia		
Ketoacidosis		
Immunosuppressive drugs	Steroid, 8 (25%)	
	Vinka alkaloids, 6 (19%)	
	Etoposide, 6 (19%)	
	Cytosine arabinoside, 16 (50%)	14 patients were taking anthracycline and cytosine arabinoside together
	Anthracycline, 15 (47%)	
Involved gastrointestinal sites	Ileum alone, 6 (18.7%)	
	Colon alone, 8 (25%)	
	Jejunum alone, 3 (9%)	
	Stomach, 5 (15.6%)	
	Duodenum, 5 (15.6%)	
	Esophagus, 4 (12.5%)	
	Appendix, 1 (3.1%)	
	Ileum and jejunum, 6 (18.8%)	
	Ileum, jejunum, and colon, 2 (6.3%)	
Findings in computed tomography	Thickening of the intestinal wall, 7 of 13 patients (53.8%)	
	Intestinal perforation, 2 of 12 patients (16.7%)	
	Intraabdominal abscess, 2 of 30 patients (6.7%)	
	Ileus, 5 of 11 patients (45%)	

ences of each manuscript were checked to prevent duplicated cases.

Patients with PGA proven by histo-pathological and/or culture methods were included, while ones with gastrointestinal involvement due to disseminated disease and oral or pharyngeal aspergillosis were excluded from our study.

A total of 20 manuscripts and 31 cases were found in the literature [6-25].

General characteristics of the patients

Thirty-one patients (19 male, 12 female, mean age between 18 and 49 years) with PGA were found in the literature [6-25]. Details of the characteristics of the patients are presented in Table 1.

Underlying diseases and immunosuppressive drugs used prior to development of PGA

The most common underlying disease was hematologic malignancy (25 cases, 78.1%). Five of these patients had also undergone allogeneic HSCT and one patient had undergone autologous HSCT due to Wilms' tumor. The most commonly used drugs prior to development of PGA were cytosine arabinoside (16 cases, 50%) and steroids (8 cases, 25%). Four of the eight patients using steroids were neutropenic at the time of diagnosis of PGA. Nineteen patients (67.9%) were neutropenic at the time of diagnosis of PGA. PGA-associated symptoms developed after a median of 11 (min-max: 3-303) days of immunosuppressive treatment. PGA developed after 30 days (at 77, 303, and 145 days) in 3 patients. Seven patients (30.4%) had bacteremia concomitantly or before the development of PGA.

Symptoms

The patients were suffering from abdominal pain, (17 of 23 patients, 72%), diarrhoea, (6 of 23 patients, 26.1%), vomiting (8 of 23 patients 34.8%), and dysphagia (2 of 23 patients 8%).

Clinical findings

Ileus (5 of 22 patients, 22.7%), acute peritonitis (3 of 23 patients, 13%), and gastrointestinal bleeding (9 of 23 patients, 39.1%) were discovered in the patients.

Aspergillus dissemination from the gastrointestinal system

Aspergillus infection spread to the lung and brain in 1 patient and only to the lung in 6 patients.

Diagnostic methods

Fungus culture (13 of 18 patients, 72%), pathologic examination (27 of 28 patients 96.4%), fungus culture + pathologic examination (8 of 32 patients, 23%), high serum galactomannan antigen level (7 of 11 patients, 63%) were used as diagnostic methods.

Aspergillus fumigatus (9 of 10 patients, 90%) and *Aspergillus flavus* (1 of 10 patients, 10%) were isolated by fungus culture. Transmural necrosis (15 of 23 patients, 65.2%) and vessel invasion (14 of 20 patients, 60%) were seen in pathologic examination.

Diagnostic interventional procedures

Surgical resection (n=18, 56.3%), autopsy (n=4, 12.5%) and, endoscopy, (n=9, 29.1%) were used in patients.

Macroscopic appearance of intestine

Mucosal ulcer (14 of 21 patients, 66.7%), mass in the gastrointestinal system (3 of 22 patients, 13.6%), and intestinal necrosis (14 of 22 patients, 63.6%) were seen in the intestine.

Antifungal therapy

Antifungal drugs were used for a mean of 13±6 days (range 4-20). The delay of antifungal treatment was 8±4.6 days (range 4-30). Voriconazole (6 of 17 patients, 35%), amphotericin (10 of 17 patients, 59%), and anidulafungin (1 of 17 patients, 6%) were used. In 9 patients, the antifungal drug's name was not known.

Mortality

Nineteen patients (59.4%) died within 16±9.7 days (range 7-30).

■ DISCUSSIONS

In patients with PGA, the first entry site of the aspergillus spores into the body is the gastrointestinal tract and patients usually have predominant gastrointestinal symptoms [26]. Our case did not have any respiratory symptoms or any radiologic findings of aspergillosis in the lung at the beginning. However, pulmonary nodules were seen on the thorax CT on the nineteenth day of febrile neutropenia when intestinal perforation devel-

oped. *Aspergillus fumigatus* was isolated from tracheal aspirate culture during the post-operative period. With these findings, we believe that our case was PGA and that pulmonary involvement developed through a secondary spread from the gastrointestinal tract. We also believe that the presence of gastric lymphoma in our case might have facilitated the colonization and subsequently invasion of aspergillus spores into the wall of the intestines.

In the past, the most important risk factor for aspergillus infection was neutropenia [27]. However, only one third of the patients had neutropenia at the time of development of invasive aspergillosis in recent publications. This is due to increased use of other immunosuppressive drugs such as steroids [28, 29]. Our study showed that only half of the patients with PGA were neutropenic and one third of the patients were using steroids. It is known that aspergillus spores cannot invade the intact mucosa as opposed to *Candida spp.* [1]. The half of the patients with PGA were using cytosine arabinoside that often causes mucositis and disruption of mucosal integrity [30]. We think that mucosal problems due to cytosine arabinoside and other immunosuppressive drugs may have great significance in the pathogenesis of PGA.

Invasive aspergillosis in allogeneic stem cell transplant cases may exceed 20%, but this ratio is reported to be as low as 2-6% in autologous HSCT cases [31, 32]. The most important risk factor for invasive aspergillosis is known as neutropenia lasting over 21 days [27]. The risk of aspergillosis in autologous HSCT cases is low due to their neutropenia period lasting less than 14 days. Our patient is an interesting case if we consider that invasive aspergillosis rarely occurs after autologous HSCT. We think that neutropenia and lymphopenia that had occurred after two cycles of ICE protocol might have contributed to the development of PGA. Our case had also received 6 cycles of R-CHOP treatment 1 year before HSCT. It is known that rituximab in this regimen reduces the number of B cells and this decrease usually resolves within 1 year [33]. It is known that B lymphocytes do not only contribute to immunity by secretion of antibodies, but also affect the functions of Th lymphocytes with produced cytokines [33]. Rituximab used a year before may have contributed to the development of the PGA.

As in invasive pulmonary aspergillosis, the most

common underlying disease was haematological malignancies in the patients with PGA [1].

PGA often manifests itself with non-specific clinical and radiological findings. It is quite natural that these nonspecific clinical and radiological findings may be confused with other diseases such as necrotizing enterocolitis, gastrointestinal GVHD, and *Clostridium difficile* enterocolitis which are more common than PGA in neutropenic patients. We excluded the clostridium colitis in the differential diagnosis of our case because our patient had no diarrhoea. GVHD could not develop in a patient that has undergone autologous stem cell transplantation. But we could not exclude necrotizing enterocolitis caused by facultative anaerobe bacteria. However, despite the effective antibiotic treatment for the microorganism isolated from blood and the improvement of neutropenia on the eighth day, the persistence of gastrointestinal symptoms and ileus should be a warning sign of atypical issues such as PGA. The abdominal CT of the present case showed the thickening of the jejunum wall and this was a non specific finding. In our case, an endoscopy accessing the jejunum could allow us to diagnose the PGA early. Because of the rare occurrence of PGA and its non specific clinical and radiological findings, a vast majority of patients may have a delayed or no antifungal treatment at all. Inadequate or delayed antifungal treatment may have a role in high mortality in patients with PGA.

The most frequently involved sites reported in literature are the ileum, jejunum, and colon in patients with PGA, but this finding may be misleading since the entire gastrointestinal tract has not been evaluated in terms of aspergillus infection in all cases. Colon, stomach, and oesophagus aspergillosis are easier to diagnose than ileum and jejunum aspergillosis because they are easily accessible by endoscopy. Therefore, most patients with PGA were diagnosed through surgical resection and autopsy.

In the literature, serum galactomannan levels were found to be high in some patients with PGA [34]. In immunodepressed patients with gastrointestinal symptoms and high body temperature who do not have pulmonary or paranasal sinus aspergillosis, we think that high serum galactomannan levels may be helpful in suggesting PGA if we take into consideration the cases in the literature. We did not measure serum galactomannan

levels in our patient because of the lack of lung-related symptoms and radiological findings.

In the majority of patients with PGA, macroscopic examination revealed mucosal ulcers and necrosis and histopathological examination revealed transmural necrosis and vascular invasion of mould hypha branching at a 45-degree angle. PGA was diagnosed in 72% of cases by microbiological identification of microorganism and pathological examination revealed hyphae structures compatible with aspergillus in almost all cases. Microorganisms can be observed in tissue samples as narrow as 3-6 microns wide, septated hypha with dichotomous acute angle (45°C) branching in the setting of invasive aspergillosis [35]. However, some hyaline mould, including *Scedosporium spp* and *Fusarium spp*, have the same appearances as *Aspergillus spp* in histopathologic examination. Thus, it is important to confirm *Aspergillus spp* by methods such as culture or polymerase chain reaction. We observed mould hypha which is compatible with aspergillus in tissue section in our case, but we did not use microbiologic methods in the diagnosis because we did not consider PGA in the preliminary diagnosis. Therefore, it is difficult to say that the fungus that invades the intestines is definitely *Aspergillus spp*. Our patient had no symptoms related to the lungs, and thorax tomography was normal at the beginning and on the sixth day of FNE attack. However, radiological findings compatible with aspergillus infection appeared and *Aspergillus spp*. was isolated from tracheal aspirate samples when neutropenia improved and intestinal perforation occurred. For this reason, pulmonary infection was thought to be caused by secondary spreading of the infection from the gastrointestinal tract. Based on the results of the isolation of *Aspergillus spp*. from the tracheal aspirate sample and fungal hyphae seen in the pathological examination of the intestinal biopsy, we thought that *Aspergillus spp*. was the causative agent of the intestinal lesion.

One of the main characteristics in the pathogenesis of aspergillus infection is tissue necrosis due to vascular invasion [1]. It is the reason for serious complications such as ileus and intestinal perforation and for a high rate of surgical intervention in such patients.

Similarly to invasive pulmonary aspergillosis, the most commonly isolated aspergillus species in PGA is *Aspergillus fumigatus* [1].

To conclude, PGA is a rare condition with non-

specific clinical and radiological findings, and it should be suspected in immunosuppressive patients with gastrointestinal symptoms who are non-responsive to antibacterial treatment.

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