Phycomycosis in Intestine Complicated with Acute Leukemia: Report of a Case

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Summary

During the course of acute lymphogenous leukemia, obstructive ileus developed to be operable. Phycomycosis was detected histologically in the resected intestinal wall and mesenteric tissue. No other etiological agents could be detected. The cause of invasion of phycomycosis was considered to be due to the immunosuppressed status of the patient. Surgical removal of the infected area and successful antifungal treatment prevented the fungal dissemination.

Introduction

Ubiquitous fungal organism of the class *Phycomycetes*, generally called “**Mucor**” has been usually considered to cause fatal disease, phycomycosis. In most reported cases of phycomycosis, central nervous system and lung have been easily affected in patients with diseases such as diabetes or malignancies¹⁰⁾¹¹⁾¹⁵⁾. Intestinal phycomycosis among various types of phycomycosis has been reported to be unusual⁴⁾⁶⁾¹⁴⁾, and almost of the cases reported have been made diagnosis only at autopsy²⁾⁴⁻⁶⁾¹¹⁾¹³⁻¹⁵⁾. Recently, prevalence of intensive chemotherapy using antibiotics and anticancer agents, or steroid therapy have been applied in patients with lymphoreticular malignancies. Subsequently considerable attention has been paid to the complication of opportunistic fungal infection in those immunosuppressed patients⁵⁾⁷⁾⁸⁾¹⁹⁾²¹⁾.

We report here that a patient of acute lymphogenous leukemia could be made to diagnose intestinal phycomycosis at the surgical operation of acute ileus, and resection of the affected intestine and antifungal chemotherapy with clotrimazole and amphotericin B prevented the patient from the further dissemination of phycomycosis.

Case report

K. K., a nineteen year-old man, was admitted to the Tokushima University Hospital on March 24, 1975, because of fever and anemia. The patient had previously been well and there was no history of diabetes. He began to notice arthralgia in both knees and elbows in the beginning of the January of this year, followed by fatigability. Four weeks prior to admission he had total amount of 2,600 ml of blood transfusion because of severe anemia and thrombocytopenia, but he had not received any kinds of anticancer agents before the admission. Since around February, generalized lymphadenopathy had

developed, which was associated with stomatitis, thirst, hematuria and facial edema. On admission he had high fever and tarry feces. White blood cell count showed 161,400 per cubic millimeter (band 0.5%, seg 1.0%, eosino 0%, baso 0%, mono 0%, lym 7.0%, lymphoblast 91.0%, myelocyte 0.5%). Immunological examination; *in vitro* lymphocyte blastogenic response to mitogens (phytohemagglutinin and pokeweed mitogen) was very low, and spontaneous rosette-forming cell to sheep red blood cells: 0%, immunoglobulin bearing cells in peripheral lymphocyte population: (Ig-M+Ig-G+Ig-A) bearing cell 4%, Ig-G bearing cell 6%, Ig-M 1%, Ig-A 1% respectively. Serum immunoglobulin level: Ig-M 99 mg/dl, Ig-G 1,600 mg/dl, Ig-A 116 mg/dl. Skin test showed negative PPD response and markedly impaired skin reactivity to phytohemagglutinin (PHA)¹⁷⁾. The diagnosis of acute lymphocytic leukemia was established by demonstration of leukemia cells in the peripheral blood and bone marrow. For the first 2 weeks after the admission he was treated with 70 mg of prednisolone three times a day and then daunomycin 40 mg/day was administered intravenously on the consecutive four days (Fig. 1). Subsequently the marked reduction on number of lymphoblast was noted. On April 4, he developed fever by 38.6°, and his white blood cell count showed 1,900 per cubic millimeter (absolute granulocyte 304 per cubic millimeter). Blood culture was positive for *Staphylococcus aureus*. Treatment with sulbenicillin (SB-PC) with doses of 4 to 6 g per day was performed from April 4 to April 15, but slight fever remained.

Fig. 1. Clinical course of a 19 year old boy with acute lymphocytic leukemia. OP: operation

Fig. 2. Part of ileus, showing areas of dark hemorrhagic necrotic ileum.

Fig. 3. Cut section of ileum, showing necrotic focus due to phycomycosis.

On April 16, abdominal pain suddenly occurred and it increased rapidly. On the next day his continuous abdominal pain was localized to the lower abdominal region and was associated with nausea. The abdomen distended markedly and he complained severe tenderness. X-ray examination showed gas and fluid levels which was characterized as acute ileus. On April 18, platelet transfusion separated from 2,000 ml of fresh blood was performed because of his thrombocytopenia, and then resection of affected part of ileum was performed at the surgical department. The resected ileum was shown in Fig. 2,3. On microscopic examination of the resected parts, branching, non-septae fungal hyphae with variable width (approximately 10 to 20 μ) as shown in Fig. 4 was found in the mesenteric tissue and muscular zone of ileum by periodic acid shiff staining. Numerous hyphae could be also seen in the affected lumina and vessel walls (Fig. 5). Fungal culture was unable to be done. However, width and structure of

Fig. 4. Typical large non-septae hyphae within mesenteric tissue. Hematoxylin and eosin stain, original magnification $\times 220$.

Fig. 5. A mesenteric blood vessel containing of hyphae within the lumen and wall. Hematoxylin and eosin stain, original magnification $\times 220$.

hyphae were defined as a kind of phycomycetes by histological observation. Immediately after the diagnosis of intestinal phycomycosis was established, antifungal agents such as clotrimazole (Bayer) (total dose, 13.5 g) and amphotericin B (total dose, 120 mg) were administered to the patient from April 23 to May 12. At the same time carbenicillin (CB-PC), 9 g per day and after May 6, cefazolin (CEZ), 6 g per day were injected intravenously. On the 31st postoperative day, fever disappeared and general condition tended to be better. White blood cell count was 3,200 per cubic millimeter (absolute granulocyte 1,088), platelets 8.7×10^4 per cubic millimeter, CRP negative, erythrocyte sedimentation rate 22 mm in one hour. He appeared to be quite well. However, skin reactivity to PHA remained suppressed. Since around 45th postoperative day, leukemia exacerbated again and died of leukemia on the 80th postoperative day in spite of intermittent combination chemotherapy such as AMP (adriamycin, 6-mercaptopurine and prednisolone), and DCMP (daunomycin, cytosine arabinoside, 6-mercaptopurine and prednisolone). On autopsy, the macroscopic examination showed: 1) swelling of systemic lymph-nodes, liver, tonsils and spleen, 2) hemorrhage in skin, epicard, lungs, renal pelvis, intestine and urinary bladder, 3) congestion of lungs, 4) peritonitis fibrosa, 5) cystitis purulenta and proctitis, 6) postoperative state of ileoileostomia. With very careful microscopic examination fungal hyphae in every changed tissues were negative. Infiltrations of leukemia cells were noted in lymphnodes, liver, spleen, renal

cortex, perivascular region of lungs and meninges, and endocardium in heart. Hemorrhage, necrosis and bacterial colony were noted in the skin of right hand.

Discussion

Opportunistic fungal infections complicating leukemia and hematological malignancies have been reported very frequently in the literature, and administration of large amount of steroid hormone and anticancer agents, or antibiotics have been considered to be major factors of inducing the fungal infection in patients with neoplastic diseases, especially lymphoreticular malignancies²⁾⁵⁾⁷⁾⁸⁾¹⁹⁻²¹⁾.

Phycomycosis is considered to be a systemic infection and frequently fatal disease. It is usually diagnosed at autopsy. In the most reported cases, phycomycosis seems to occur preferably in patients with leukemia¹⁸⁾ and this fact indicates that immunodeficient state due to leukemia may be an inducing factor to this fungal infection. On the other hand, the commonest preceding infections have been reported to be caused by *Staphylococcus aureus* and *Pseudomonas aeruginosa*¹⁸⁾. In this case bacteremia due to *Staphylococcus aureus* was preceded to the phycomycosis.

It is difficult and unusual to diagnose phycomycosis during life, but success in treating phycomycosis with amphotericin B has been reported in some well-controlled diabetic patients, and in an acute leukemic patient with biopsy-proved pulmonary phycomycosis¹⁾¹²⁾¹⁸⁾. Diagnosis of intestinal phycomycosis showing ileus of ileum happened to be made after surgical resection in this case. Thereafter administration of antifungal agents such as amphotericin B and clotrimazole seems to prevent the systemic infection due to *Phycomycetes*. These antifungal chemotherapy has been reported to be effective for treating the fungal infection with *Aspergillus* or *Candida*⁹⁾¹⁶⁾. The patient finally died of leukemia but at autopsy any kinds of fungal elements could not be detected microscopically.

We checked immunological status of this patient during the course of illness by rosette-forming cells to sheep red blood cells (thymus-derived lymphocytes), *in vitro* and *in vivo* responses to PHA for knowing host cellular immunocompetence. Cellular immunodeficient state was noted on his admission indicating that there were depressed skin responses to PHA and PPD, and decreased blastogenic reactivity of lymphocytes to PHA with reduced number of rosette-forming cells, but normal levels of various serum immunoglobulins. Since *in vivo* skin reactivity to PHA reflects general immunocompetence of host including cellular immunity¹⁷⁾¹⁸⁾, skin reactivity to PHA was measured sequentially during the course. Subsequently impaired skin reactivity to PHA was noted in every test before the diagnosis of phycomycosis. This indicates that depressed cellular immunity might also play an important role to induce fungal infection¹⁸⁾. On the other hand leukocytopenia seems, of course, to be most inducing factor to fungal infection¹⁸⁾. In this case leukocytopenia, particularly mature granulocytopenia after the usage of steroid hormone and daunomycin is considered to be the other major etiologic factor for the phycomycosis.

Further studies on the role of cellular immunity on the fungus infection including phycomycosis is required.

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