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Successful Treatment of Systemic Geotrichum capitatum Infection by Liposomal Amphotericin-B, Itraconazole, and Voriconazole in a Japanese Man
(Liposomal amphotericin-B、itraconazole、voriconazoleによる全身性Geotrichum capitatum感染の治療が奏効した日本人男性の1症例)

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Successful treatment of systemic *Geotrichum capitatum* infection by liposomal amphotericin-B, itraconazole, and voriconazole in Japanese case

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Short titile: Successful treatment of systemic Geotrichum capitatum infection

Abstract

Severe systemic *Geotrichum capitatum* (*G. capitatum*) infection is rare, especially in Japan. *G. capitatum* infection has been reported mainly in immunocompromised patients and the prognosis is poor with a mortality rate of approximately 50–75%. We here report a Japanese case of systemic *G. capitatum* infection in a severe neutropenic patient who was receiving chemotherapy for acute myelogeneous leukemia with multilineage dysplasia. *G. capitatum* was isolated from blood cultures, and was also formed multiple nodular lesions in lung fields. The infection was successfully cured with a combination of amphotericin B, itraconazole, and voriconazole.

Key words

Geotrichum capitatum; acure myelogeneous leukemia (AML); amphotericin B; itraconazole; voriconazole

Introduction

Patients who receive intensive chemotherapy especially for hematological malignancies such as acute leukemia experience neutropenic periods that entail a high risk of fungal infections. Those fungal infections are usually caused by *Candida* and *Aspergillus* species, although many other molds and yeasts have emerged as causes of invasive infections and the prevalence of infectious fungi has been increasing in the recent years.

Invasive systemic *Geotrichum capitatum* (*G. capitatum*) infection is rare, and has been reported exclusively in immunocompromised patients, particularly those receiving intensive chemotherapies for hematological malignancies such as acute leukemia [1-4]. *G. capitatum*, formerly known as *Trichosporn capitatum* or *Brastochizomyces capitatus*, is an anamorph of *Dipodascus capitatus*, so that *Dipodascus capitatus* is a taxonomic teleomorph of *G. capitatum* [5]. Despite intensive antifungal therapy, the mortality rate is approximately 50–75% [1, 2]. Emergence of *G. capitatum* is predominantly in European countries, particularly in Mediterranean areas [1]. We here report a Japanese case of systemic *G.*

capitatum infection in a severely neutropenic patient with acute myeloid leukemia with multilineage dysplasias. He was cured of that infection with a combination of liposomal-amphotericin-B (L-AMPH-B), itraconazole (ITCZ) and voriconazole (VRCZ).

Case Report

A 64-year-old Japanese man who had consulted a physician because of liver dysfunction was referred to our department because of anemia and thrombocytopenia in September 2006. Bone marrow aspiration was performed, and he was given a diagnosis of myelodysplastic syndrome (MDS) (refractory anemia with excess blasts (RAEB) -2). He was admitted to our hospital because of leukemic evolution of MDS. The laboratory data on admission showed that his WBC was 13.17 x 10^9 /L, with a differential of 24% neutrophils, 10% lymphocytes, 3% monocytes, 0% eosinophils, 1% basophils, and 61% blasts. The hemoglobin concentration was 99 g/L with a mean corpuscular volume of 106.6 fL indicating mild macrocytosis. The platelet count, 48 x 10^9 /L, revealed thrombocytopenia. Biochemical data included an elevated AST of 93 IU/L, ALT of 109 IU/L, γ-GTP of 147 IU/L (normal range: 4-67 IU/L), lactate dehydrogenase (LDH) of 402 IU/L (105-210 IU/L), CRP of 0.44 mg/dL (<0.3 mg/dL), and serum ferritin of 1300 ng/mL. β-D-glucan was <0.5 pg/mL, within the

normal range.

Bone marrow aspiration showed a marked increase of blasts, 51% of all nucleated cells. Blasts were slightly positive for peroxidase and had nucleoli. Many blasts had vacuoles in their cytoplasm. He was diagnosed as having acute myelogenous leukemia with multilineage dysplasia with prior MDS RAEB-2.

Induction therapy consisting of idarubicin 12 mg/m^2/day on days 1-3 and cytarabine 100 mg/m^2/day c.i.v. on days 1-5 was administered via central venous catheter. Antifungal prophylaxis was performed by administration of 200mg/day of fluconazole (FLCZ) from his admission. Unfortunately, remission was not achieved by first induction therapy.

A second induction therapy was then performed using mitoxantrone 7 mg/m^2/day on days 1-3 and cytarabine 200 mg/m^2/day c.i.v. on day 1-5 via the same central venous catheter. FLCZ had been administered for 41 days, but then changed to 150mg/day of micafungin (MCFG) from day 2 of second induction therapy because β-D -glucan slightly increased to 15.5 pg/mL. His WBC decreased to 0.1/L on day 16, and a fever exceeding 38 ^{o}C developed during the neutropenic phase

despite prophylaxis with MCFG. β-D-glucan increased to 78 pg/mL. Computed tomography (CT) showed many nodular shadows approximately 10 mm in size in both lungs (Fig. 1). No obvious abscess was detected in liver or spleen by abdominal CT scan. The possibility of fungal infection was confirmed by blood culture taken on day 18 in potato dextrose and CHROM agar. White-pink and wrinkled colonies were observed on CHROM agar. Yeast-like fungi which multiplying mainly by arthroconidia and partly by annelloconidia were observed, but brastconidia were not observed. The fungi were then cultured on Sabouraud dextrose agar and identified using the commercially available fungus identification system ATB API ID 32 C (SYSMEX bioMérieux Co.,Ltd., Tokyo, Japan). The sugar requirements led to the final diagnosis of *G. capitatum*.

Susceptibility testing using yeast-like fungi FP Eiken trays（Eiken Chemical Company, LTD., Tokyo, Japan）showed low minimum inhibitory concentrations (MIC) for amphotericin B (AMPH-B), 5fluorouracil, ITCZ, and VRCZ, but the MIC for fluconazole and MCFG, both of which had been used for prophylaxis purpose, were high (Table 1).

Neutropenia was recovered on day 27, and MCFG was replaced by 215 mg/day of liposomal AMPH-B (L-AMPH-B) on day 28 because of the MIC informations. (The period of MCFG administration was 27 days.) Although central venous catheter could not be removed or substituted by new catheter because of the risk of bleeding, his fever declined in accompaniment with a decrease in β-D-glucan. However, his fever rose after second consolidation therapy was initiated, so that ITCZ was added to the regimen on day 35. ITCZ appeared to be effective, but was accompanied by severe diarrhea so was discontinued. Total period of ITCZ administration was 13 days. Fever declined again after stopping ITCZ administration, but mild renal dysfunction, indicated by a serum creatinine of 1.6 mg/dl, developed. L-AMPH-B was therefore discontinued, and 2.5 mg/kg of VRCZ intravenously was substituted. The total period of administration of L-AMPH-B was 50 days. Nodular shadows in lung fields disappeared by CT, and *G. capitatum* was no longer detected in blood culture after this change in therapy. Clinical course is shown as Fig. 2. Although direct evidence of *G. capitatum* infection from lung lesions could not obtained, we thought that lung lesions were

also *G. capitatum* lesions because the lesions appeared with the increase of β-D-glucan and disappeared by antifungal treatment.

After this remission was achieved several courses of chemotherapy should have been administered because his disease activity had not been controlled well and he often experienced high fever, therefore, administration of VRCZ orally had been kept continued and no evidence of recurrence of *G. capitatum* infection was observed until he succumbed to leukemia about one year later.

Discussion

G. capitatum infection is an uncommon fungal infection, especially in Japan. This filamentous fungus is found in soil, and frequently isolated from human skin, respiratory and digestive tracts [1]. Colonization in those sites sometimes leads to secondary localizations via hematogenous dissemination mainly in the lung, liver [4, 6]. Invasive *G. capitatum* infection is relatively rare, approximately 100 cases having been reported [1, 3, 4, 7, 8]. Risk factors for systemic *G. capitatum* infection have been reported to be prolonged neutropenia, intensive chemotherapy, the use of broad-spectrum antibacterial agents and local disruption of skin and mucosal defenses [2, 9-11]. Therefore, systemic *G. capitatum* infection is prone to occur in neutropenic patients with hematological malignancies such as acute leukemia, because patients receiving intensive chemotherapy, experience severe long neutropenic periods, and are often placed on a central venous catheter. Patients with conditions other than hematological malignancies are also susceptible to systemic infection by *G. capitatum*; an outbreak in an intensive care unit has been reported [3].

The diagnosis may usually be made by blood culture [4, 7]. *G.*

capitatum was detected by blood culture in the present case, but lung should also be involved even though without any pathological or mycological evidence, so that the route for the infection of *G. capitatum* was not clear. *G. capitatum* might have been in lung as colonization and increased in the neutropenic period during chemotherapy, and then go into the blood stream and systemic infection was completed. However, it was also likely that systemic infection of *G. capitatum* cause secondary disseminations in lung fields, because there were multiple small lesions in bilateral lobes of lung determined by CT. The multiple nodular shadows revealed by chest CT in the present case might be similar to the previous reports, but there have been no clear explanation for the mechanism of formation of multiple lesions in lung [2, 4]. Another possibility was that *G. capitatum* might invade from skin via central venous catheter, and increased in the blood stream, and then finally lung lesions were appeared as dissemination. There is also a possibility that *G. capitatum* invaded as translocation from the gastrointestinal tract, but it was difficult to confirm that because there seemed to be no obvious abscess in liver or spleen.

The prognosis of disseminated *G. capitatum* infection has been

reported to be extremely poor, with a mortality rate of approximately 50–75% despite intensive antifungal therapy with AMPH-B, ITCZ or flucytosine [1-4, 6]. Combination treatment with AMPH-B and 5-fluorocytosine has been recommended [2], as has use of novel antifungal agents such as VRCZ and caspofungin [8]. Although the patients treated with each of those new antifungal agents died [8], combination therapy with VRCZ and caspofungin may be effective for systemic *G. capitatum* infection [12, 13]. In the present case, L-AMPH-B suppressed infectious activity of *G. capitatum* . VRCZ also seemed to be effective in this case because chemotherapy had been continued without L-AMPH-B. The recovery from neutropenia may also have contributed to overcoming the infection, therefore using granulocyte colony stimulating factor (G-CSF) should be considered if the status of the infected patients permits.

In vitro susceptibility data on *G. capitatum* has been limited [14-16]. In a previous report AMPH-B and VRCZ showed the lowest MICs of various antifungal agents against 23 *G. capitatum* isolates *in vitro* [14]. Susceptibility to MCFG, which was used for the purpose of prophylaxis in this patient at the occurrence of systemic *G. capitatum*

infection, was low, in keeping with an another report [17], so that the continuous using of MCFG as prophylaxis should only be performed under careful observation of clinical symptoms, especially in Japan where MCFG has been widely used. Our *in vitro* susceptibility data showed that MICs for AMPH-B and VRCZ were relatively low. Therefore, the clinical effectiveness looked to be compatible with *in vitro* data in the present case. However, the correlation between *in vitro* and *in vivo* susceptibility requires further study.

We herein report a case of systemic infection by *G. capitatum*, a predominantly European pathogen, observed during chemotherapy for acute leukemia in Japan. In Japan, only few other cases have been previously reported [17, 18], and the reason for the low occurrence of *G. capitatum* in Japan has not been known now. However, the possibility that new or rare fungal pathogens might increase in prevalence like *G. capitatum* in the present case should be kept mind, because in recent years many novel agents for bacterial and fungal infections have become available and those agents might contribute to the control of many infections in Japan.

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Table 1

Antifungal agents	MIC (μg/ml)
AMPH-B	0.25
5-FC	0.12
FLCZ	8
ITCZ	0.01
MCZ	0.5
MCFG	1
VRCZ	0.12

The abbreviations used are: AMPH-B, amphotericin B; 5-FC, 5-fluorouracil; FLCZ, fluconazole; ITCZ, itraconazole; MCZ, miconazole; MCFG, micafungin; and VRCZ, voriconazole.

Figure legends

Figure 1

Computed tomography showed that many nodular shadows with approximately 10 mm in size in the lung field.

Figure 2

Clinical course of the present case. The abbreviations used are: BT, body temperature; IDA, idarubicin; Ara-C, cytarabine, MIT, mitoxantrone; FLCZ, fluconazole; MCFG, micafungin; L-AMPH-B, liposomal amphotericin B; ITCZ, itraconazole; and VRCZ, voriconazole.

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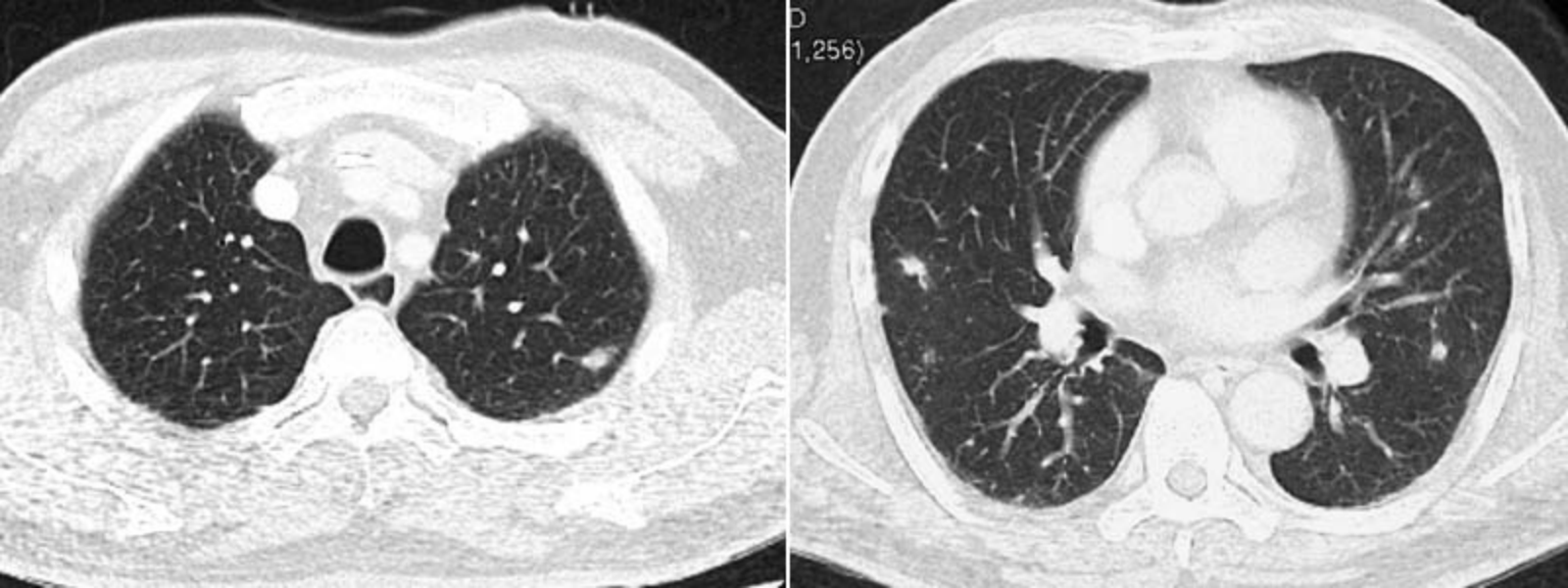
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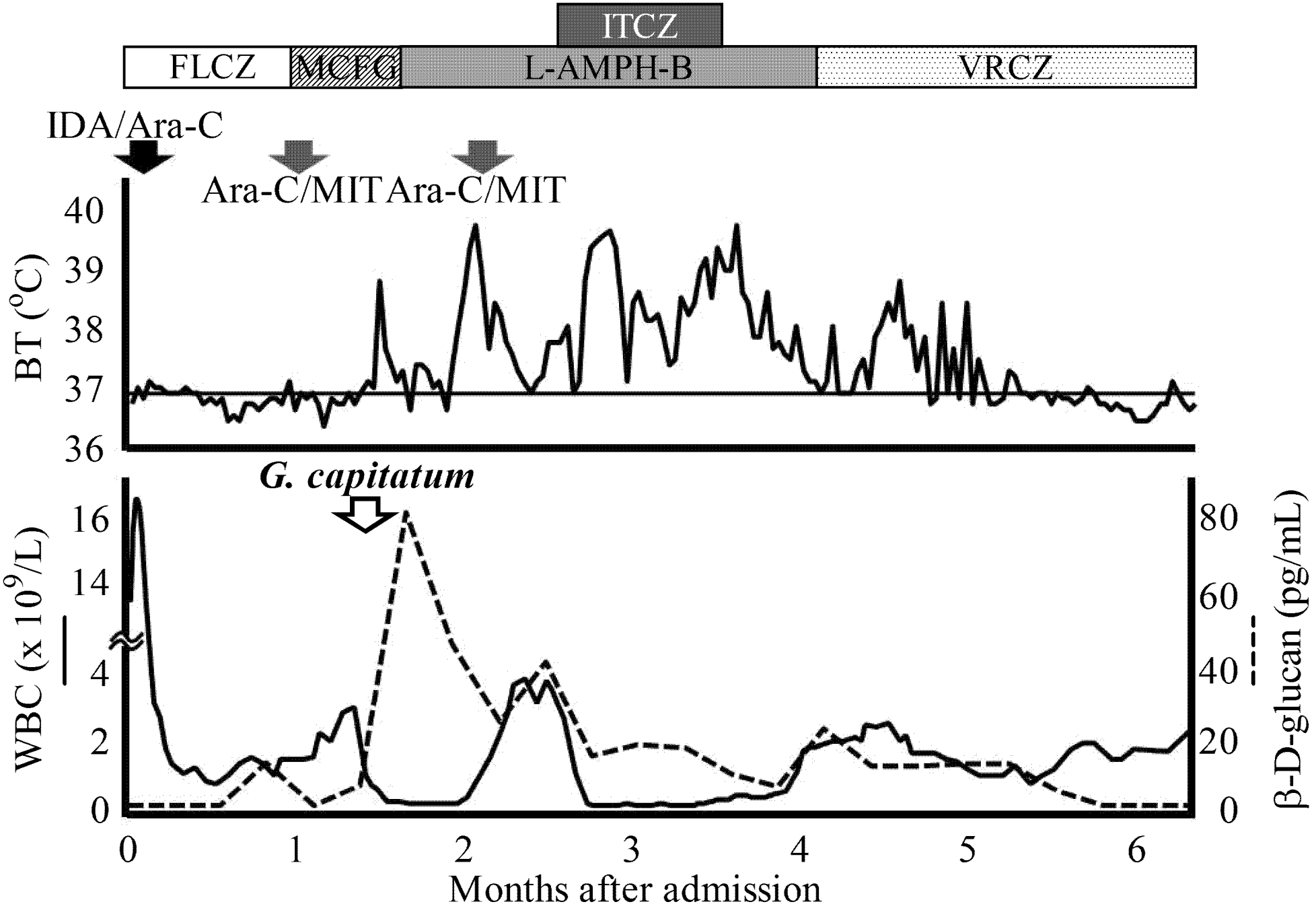
ITCZ
FLCZ
MCFG
L-AMPH-B
VRCZ
IDA/Ara-C
Ara-C/MIT
Ara-C/MIT
BT (°C)
40
39
38
37
36
G. capitatum
WBC (x 10⁹/L)
16
14
4
2
0
80
60
40
20
0
β-D-glucan (pg/mL)
0
1
2
3
4
5
6
Months after admission