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# Disseminated *Trichosporon beigelii* Infection in Patients with Malignant Diseases: Immunohistochemical Study and Review

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***Trichosporon beigelii* is a causative agent of opportunistic infection and summer-type hypersensitivity pneumonitis in Japan. However, as the diagnosis of *Trichosporon beigelii* infection is sometimes difficult, the actual incidence of this disease may be underestimated. Of 203 autopsy patients with malignant disease, seven (7.7 %) were diagnosed with disseminated *Trichosporon beigelii* infection by immunohistochemical investigation of formalin-fixed, paraffin-embedded tissue sections. Including these seven, a total of 43 patients with *Trichosporon beigelii* infection have been reported in Japan. The majority of them had underlying hematologic malignancies, for which they received cytotoxic chemotherapy resulting in neutropenia. This study indicates that the immunohistochemical method, which can be applied to biopsy specimens, is an excellent tool for specific diagnosis of *Trichosporon beigelii* infection, which is an emerging fatal mycosis in immunocompromised patients with profound neutropenia.**

*Trichosporon beigelii* (formerly *Trichosporon cutaneum*) is a fungus causing white piedra, a superficial infection of the hair shafts commonly encountered in tropical and subtropical regions. Recently, it has been suspected as a causative agent of summer-type hypersensitivity pneumonitis in Japan (1, 2). The incidence of deep-seated or disseminated *Trichosporon beigelii* infection (trichosporonosis) has been increasing among immunocompromised patients, particularly those with hematologic malignancies undergoing intensive cytotoxic chemotherapy (3–18). Although the diagnosis of *Trichosporon beigelii* infection is confirmed by positive cultures and histopathological evidence, the former do not directly indicate invasive disease, and it is sometimes difficult to distinguish this fungus from *Candida* in tissue sections. Moreover, the situation may become more complicated in patients with polyfungal infections.

The immunoperoxidase stain was reported to be useful for the identification of *Trichosporon beigelii* in tissue sections (19, 20). We have therefore undertaken an immunohistochemical study to identify *Trichosporon beigelii* in formalin-fixed paraffin-embedded tissue sections from autopsy patients. We report here seven patients with disseminated *Trichosporon beigelii* infection diagnosed immunohistochemically and assess the validity of this method in the diagnosis of *Trichosporon beigelii* infection. In addition, we review the literature on trichosporonosis in Japan to emphasize the increasing importance and awareness of this opportunistic fungal infection in immunocompromised patients.

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## Materials and Methods

*Isolation of Trichosporon beigelii.* *Trichosporon beigelii* was isolated by culture on Sabouraud's broth medium from the blood of a patient with acute promyelocytic leukemia before he died. The isolates produced creamy, wrinkled and folded colonies, and microscopic examination revealed the presence of arthroconidia, blastoconidia, true hyphae and pseudohyphae, typical of *Trichosporon* species (Figure 1). The isolates were further identified as *Trichosporon beigelii* based on their biochemical characteristics. Isolates hydrolyzed urea and assimilated glucose, sucrose, maltose, lactose, cellobiose, galactose, starch, xylitol, L-arabinose and 2-keto-D-gluconate, but did not utilize nitrate. Susceptibility testing demonstrated the following minimal inhibitory concentrations (MICs) for the isolates: amphotericin B, 1.56 μg/ml; 5-flucytosine, 3.13 μg/ml; miconazole, 0.20 μg/ml and fluconazole, 50 μg/ml.

*Production of Antisera to Trichosporon beigelii.* *Trichosporon beigelii* was killed with 100 % ethanol and washed in phosphate-buffered saline (PBS). A Japanese white rabbit was then immunized with whole organisms of *Tri-*

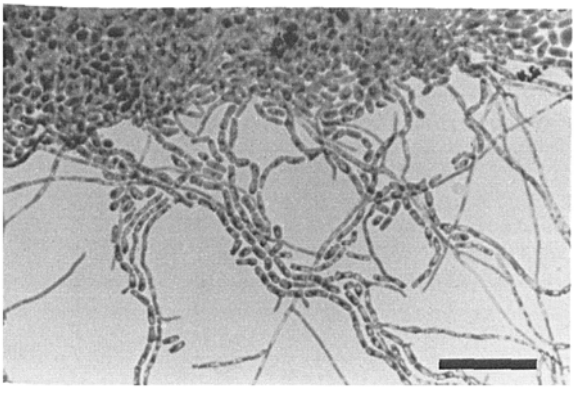

**Figure 1:** *Trichosporon beigelii* grown on Sabouraud's dextrose agar demonstrating blastoconidia, arthroconidia, pseudohyphae and hyphae. Lactophenol cotton blue mount. Bar = 25 μm.

*chosporon beigelii* (2.24 x $10^7$ organisms) by four weekly intravenous inoculations. The antibody was titrated by the immunoperoxidase method. One week after the last immunization the rabbit was exsanguinated, and the serum was stored at -70 °C after heat inactivation.

*Absorption of Antiserum. Cryptococcus neoformans*-absorbed antiserum was prepared by mixing a 1:250 dilution of rabbit antiserum to *Trichosporon beigelii* with an equal volume of suspension of formalin-killed *Cryptococcus neoformans* (5 x $10^7$ organisms). The mixture was incubated for 2.5 h in a 37 °C water bath, kept at 4 °C for 24 h, and centrifuged at 12,000 x *g* for 20 min. The supernatant was then filtered through a 0.45 μm millipore membrane. The absorbing procedure was repeated three times.

*Immunohistochemical Staining.* The autopsy tissue sections were deparaffinized through immersion in xylene and ethanol. Endoperoxidase was inhibited by soaking the sections in 0.3 % hydrogen peroxide in methanol for 30 min. After washing in PBS the slides were treated with either unabsorbed antiserum to *Trichosporon beigelii* diluted 1:5,000 with PBS or *Cryptococcus neoformans*-absorbed antiserum diluted 1:200 with PBS for 30 min. After washes in PBS the slides were reacted with biotinylated goat anti-rabbit immunoglobulins (BioGenex, USA) for 30 min.

The slides were again washed in PBS and reacted with peroxidase-conjugated streptavidin (BioGenex) for 30 min, subsequently rewashed, and covered for 10 min with 0.05 mol/l Tris-HCl buffer, pH 7.4, 0.15 mol/l NaCl containing 0.001 % hydrogen peroxide and 3-3' diaminobenzidine (0.5 mg/ml). They were counterstained with hematoxylin, dehydrated with graded ethanol, cleared with xylene and mounted. All reactions were carried out at room temperature.

## Results

*Specificity of Antiserum.* The specificity of the antiserum to *Trichosporon beigelii* was tested by indirect immunofluorescence using *Trichosporon beigelii*, *Trichosporon capitatum*, *Candida albicans*, *Candida tropicalis*, *Candida krusei*, *Candida parapsilosis* and *Cryptococcus neoformans*. Antiserum to *Trichosporon beigelii* was strongly reactive with *Trichosporon beigelii* and weakly reactive with *Cryptococcus neoformans* but did not react with *Candida albicans* or other fungi. *Cryptococcus neoformans*-absorbed antiserum was as reactive with *Trichosporon beigelii* as the unabsorbed antiserum but was no longer reactive with *Cryptococcus neoformans*. Antiserum specificity was also examined using the immunoperoxidase method (streptavidin-biotin-peroxidase method) in the autopsy sections from patients with defined trichosporonosis, candidiasis, cryptococcosis, aspergillosis and mucormycosis (Figure 2).

*Incidence of Trichosporon beigelii Infection.* During the ten-year period from 1983 to 1992, 203 autopsy patients with cancer, including 95 with hematologic malignancies and 108 with solid malignancies, were observed. Among them, 70 (27.7 %) had deep mycoses: 51 among those with hematologic malignancies and 19 among those with solid malignancies. An indirect immunoperoxidase method employing *Cryptococcus neoformans*-absorbed anti-*Trichosporon beigelii* antibody was used to examine formalin-fixed, paraffin-embedded tissue sections from all patients with formerly diagnosed candidiasis and from some with other fungal infections. *Trichosporon beigelii* could be successfully visualized in sections from seven patients, but indirect immunoperoxidase staining using anti-*Candida albicans* antibody (Dako, Japan) was negative. Analysis of the deep mycoses involved, including polyfungal infections, revealed candidiasis in 37 patients, aspergillosis in 28, mucormycosis in 7, trichosporonosis in 7 and cryptococcosis in 5 (Table 1).

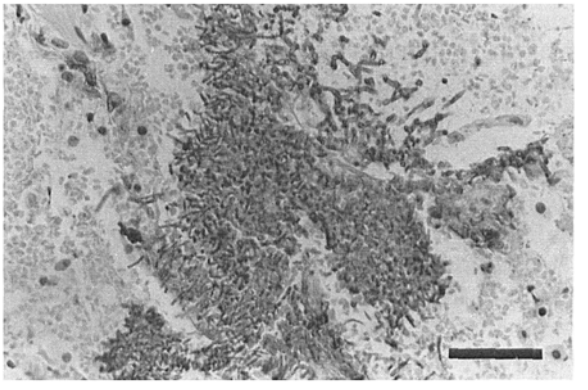

**Figure 2:** *Trichosporon beigelii* in lung tissue, stained using the immunoperoxidase method. Bar = 50 μm.

**Table 1:** Deep mycoses in autopsy patients with malignant disease.

| Underlying disease | No. of patients | No. (%) with mycoses | Fungal species | | | | |
|---|---|---|---|---|---|---|---|
| | | | *Candida* | *Aspergillus* | *Cryptococcus* | *Mucor* | *Trichosporon* |
| Hematologic malignancy | | | | | | | |
| Acute myelogenous leukemia | 26 | 19 (73.1) | 7 | 10 | 0 | 2 | 3 |
| Acute T-cell leukemia | 20 | 7 (35.0) | 1 | 3 | 3 | 0 | 0 |
| Acute lymphocytic leukemia | 8 | 5 (62.5) | 1 | 4 | 0 | 1 | 1 |
| Chronic myelogenous leukemia | 8 | 4 (50.0) | 2 | 2 | 0 | 0 | 1 |
| Non-Hodgkin's lymphoma | 25 | 13 (52.0) | 6 | 5 | 1 | 0 | 1 |
| Others | 8 | 3 (37.5) | 2 | 0 | 0 | 0 | 1 |
| Subtotal | 95 | 51 (53.7) | 19 | 24 | 4 | 3 | 7 |
| Solid malignancy | | | | | | | |
| Liver cell carcinoma | 45 | 4 (8.9) | 4 | 1 | 0 | 1 | 0 |
| Lung carcinoma | 31 | 8 (25.8) | 7 | 1 | 0 | 2 | 0 |
| Others | 32 | 7 (21.9) | 7 | 2 | 1 | 1 | 0 |
| Subtotal | 108 | 19 (17.6) | 18 | 4 | 1 | 4 | 0 |
| Total | 203 | 70 (27.7) | 37 | 28 | 5 | 7 | 7 |

The patients with trichosporonosis included four males and three females, with a mean age of 56 years (range 47–67 years). All had an underlying hematologic malignancy. Of them, three had acute myelogenous leukemia, one acute lymphocytic leukemia, one chronic myelogenous leukemia, one non-Hodgkin's lymphoma and one multiple myeloma. All had received anticancer chemotherapy resulting neutropenia, and profound neutropenia (< 100/μl) persisted 5 to 106 days until death in six patients. *Trichosporon beigelii* was isolated from blood in two patients before they died. Antifungal chemotherapy with amphotericin B or a combination of amphotericin B and 5-flucytosine was administered to all patients; however, trichosporonosis contributed to death in six.

*Pathologic Findings.* Macroscopically, multiple, discrete, yellow micronodules, occasionally surrounded by red rims, 0.5 to 1 cm in diameter, were seen on cut surfaces of the lungs, kidneys, liver, spleen, etc. Multiple ulcers and erosions associated with submucosal hemorrhage and hemorrhagic infarctions were seen in the gastrointestinal tract. Microscopically, numerous centrally necrotic foci with fungi arranged in a radial starburst pattern were observed (Figure 3). The cellular inflammatory reaction was minimal or absent and was occasionally associated with parenchymal hemorrhage and hemorrhagic infarctions. The fungi were clearly stained with periodic acid-Schiff and Gomori's methenamine-silver stains and exhibited both yeast-like and hyphal elements. The large pleomorphic yeast forms were predominant in the central areas, while the hyphal forms, exhibiting septates and minimal branches, and arthroconidia were seen predominantly in the invasive areas. The common sites of *Trichosporon beigelii* infection were the lungs, kidneys, gastrointestinal tract and thyroid in six patients, followed by liver and spleen in four, heart in three, and pancreas, bone marrow and lymph nodes in two (Table 2). *Trichosporon* organisms were present in ulcers of the gastrointestinal tract, and the vasculature was invaded with fungal emboli. Fungal invasion of the lungs was seen in the alveolar vessels as well as in the bronchioloalveolar space. Fungi in the kidneys

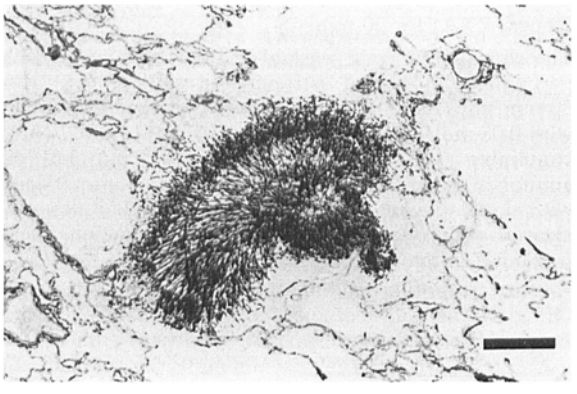

**Figure 3:** *Trichosporon beigelii* in lung tissue demonstrating a radial starburst pattern. Gomori's methenamine-silver stain. Bar = 200 μm.

**Table 2:** Autopsy findings in seven patients with disseminated *Trichosporon beigelii* infection.

| Case no. | Age in years/sex | Underlying disease | Sites of infection | Concurrent infections |
|---|---|---|---|---|
| 1 | 54/M | ALL | lung, kidney, liver, spleen, thyroid, adrenal gland, bone marrow, lymph node, skin | aspergillosis (liver) |
| 2 | 47/F | AML | lung, GI tract, kidney, liver, spleen, thyroid, heart, pancreas, bone marrow, lymph node, skin | none |
| 3 | 55/M | AML | GI tract, kidney, thyroid | none |
| 4 | 53/F | CML | lung, GI tract, kidney, thyroid | none |
| 5 | 59/M | NHL | lung, GI tract, kidney, liver, spleen, thyroid, heart, pancreas | aspergillosis (lung, kidney, brain), candidiasis (esophagus) CMV infection (thyroid, pancreas), HSV infection (esophagus) |
| 6 | 67/F | MM | lung, GI tract, liver, skin | none |
| 7 | 60/M | AML | lung, GI tract, kidney, liver, spleen, thyroid, heart | none |

ALL = acute lymphoblastic leukemia; AML = acute myelogenous leukemia; CML = chronic myelogenous leukemia; NHL = non-Hodgkin's lymphoma; MM = multiple myeloma; CMV = cytomegalovirus; HSV = herpes simplex virus; GI = gastrointestinal.

were located predominantly in the glomeruli, more so than in the tubules. Concurrent infection with *Aspergillus* was observed in patients 1 and 5. In patient 5, *Candida*, cytomegalovirus and herpes simplex virus infections were also present simultaneously. *Candida* was identified only in the esophagus, by an immunoperoxidase staining method using anti-*Candida albicans* antibody (Dako); the blood culture was negative for *Candida albicans*.

## Discussion

Some fungi previously considered contaminants are emerging as causative pathogens in immunocompromised hosts receiving intensive cytotoxic chemotherapy and extended courses of antibiotics (12). *Trichosporon beigelii*, as one of these fungi, is a normal inhabitant of soil and is occasionally found as part of the normal cutaneous and throat flora in humans (21, 22). Disseminated trichosporonosis due to *Trichosporon beigelii* is an uncommon but emerging mycosis, which is often difficult to diagnose, refractory to treatment, and associated with a high attributable mortality.

The first reported case of deep trichosporonosis was described in 1970 in a 39-year-old woman who presented with a brain abscess due to *Trichosporon beigelii* (3). In recent years an increasing number of reports of trichosporonosis, particularly among patients with acute leukemia, have appeared (4–18). However, the actual incidence of disseminated trichosporonosis may be underestimated due to diagnostic difficulty. The diagnosis of *Trichosporon beigelii* infection is confirmed by positive cultures and histopathological evidence. However, positive surveillance cultures do not directly indicate invasive disease because of the possibility of colonization. On the other hand, the absence of positive cultures does not exclude a diagnosis of invasive trichosporonosis. The problem becomes more complicated in patients with polyfungal infections, because the distinction of *Trichosporon* from *Candida*, the most common causative pathogen of deep mycosis, in tissue sections is sometimes difficult. Evans et al. (5) reported that *Trichosporon* in tissue sections was suggested by the presence of both yeast-like and hyphal elements. *Candida* as well as *Trichosporon* shows both forms, but *Candida* yeasts and hyphae in tissue rarely exceed 4 μm in diameter, whereas both forms of *Trichosporon* measure up to 10 μm. Moreover, *Trichosporon* shows a radially arranged pattern of fungal growth and

the presence of arthroconidia. Another fungus likely to be confused with *Trichosporon* is *Geotrichum*. Both fungi produce arthroconidia in tissue, but *Geotrichum* is distinguished from *Trichosporon* by its failure to form blastoconidia.

We realize that it is rather difficult to distinguish *Trichosporon* from *Candida* according to the above criteria. As other researchers report, *Trichosporon beigelii* infection does occasionally occur in patients with profound neutropenia due to cytotoxic chemotherapy (9–12). The incidence of trichosporonosis at our institute is 7.7 % among autopsy patients with hematologic malignancies, and this infection constitutes 13.7 % of deep mycoses. The fact that six of seven patients in our series had been previously misdiagnosed with candidiasis also suggests a general underdiagnosis of trichosporonosis. The results of our study also demonstrate that the immunohistochemical method is an excellent tool for precise and specific diagnosis of *Trichosporon beigelii* infection.

McManus and Jones (23) described a patient with disseminated *Trichosporon beigelii* infection in whom the latex agglutination test for *Cryptococcus neoformans* (LATC) in serum was falsely positive, and suggested the utility of the LATC for diagnosis. Melcher et al. (24) developed a model of disseminated *Trichosporon* infection in persistently granulocytopenic rabbits. They demonstrated that antigenemia, as an early manifestation of disseminated *Trichosporon* infection, originated in vivo from a fibrillar extracellular matrix extending from the cell wall of the organism. However, the LATC in serum may be negative in patients receiving amphotericin B (25). In our series the LATC in sera was positive in two patients but was negative in two others who were receiving antifungal chemotherapy. Thus, the sera of some patients with disseminated trichosporonosis react positively in the LATC, but a negative LATC in serum does not eliminate a diagnosis of invasive trichosporonosis, especially when the patients have been receiving antifungal drugs.

Including the present series, a total of 43 Japanese patients with disseminated *Trichosporon beigelii* infection have been reported in the literature (Table 3) (26–30). The patients' mean age was 51 years (range 2–84 years); 31 were males and 12 females. Thirty-seven (86 %) of these 43 patients had underlying hematologic malignancies, mainly acute myelogenous leukemia. Cytotoxic chemotherapy induced a neutropenic state and caused profound neutropenia (< 100/μl) in most patients. Other patients with non-malignant diseases, such as chronic renal failure or drug-induced pneumonitis, had been administrated corticosteroids, but a 2-year-old girl who developed *Trichosporon beigelii* meningitis did not have any distinctive underlying disease. *Trichosporon beigelii* was isolated from 32 patients while they were alive, while others were diagnosed at autopsy. Antifungal chemotherapy, mainly with amphotericin B, was administered to 37 patients, but only five recovered. *Trichosporon beigelii* is also a causative allergen for hypersensitivity pneumonitis, which commonly develops during the summer in Japan (1, 2). Disseminated trichosporonosis, on the other hand, develops throughout the year.

The present findings and the literature reviewed support the widely held view that persistent profound neutropenia and previous treatment with cytotoxic chemotherapeutic agents, corticosteroids and broad-spectrum antibiotics are predisposing risk factors for disseminated tricho-

**Table 3:** Characteristics of 43 patients with disseminated *Trichosporon beigelii* infection in Japan.

| Characteristic | No. of patients |
|---|---|
| Underlying disease | |
| Acute myelogenous leukemia | 15 |
| Acute lymphoblastic leukemia | 4 |
| Chronic myelogenous leukemia | 4 |
| Non-Hodgkin's lymphoma | 6 |
| Malignant histiocytosis | 2 |
| Myelodysplastic syndrome | 3 |
| Multiple myeloma | 2 |
| Aplastic anemia | 1 |
| Lung carcinoma | 2 |
| Chronic renal failure | 2 |
| Drug-induced pneumonitis | 1 |
| None | 1 |
| Concurrent therapy | |
| Combination chemotherapy | 31 |
| Steroids | 6 |
| None | 3 |
| Not described | 3 |
| Neutropenia (< 100/μl) | |
| Yes | 26 |
| No | 4 |
| Not described | 13 |
| Onset | |
| May-October | 16 |
| November-April | 18 |
| Not described | 9 |
| Outcome | |
| Died/recovered | 38/5 |

sporonosis. In the study by Walsh (31), disseminated trichosporonosis reported in 55 (82 %) of 67 patients most frequently involved the lungs, kidneys, skin, liver, spleen and heart, whereas localized deep visceral trichosporonosis was identified in 12 (18 %) of 67. In our series all patients had disseminated trichosporonosis involving the lungs, alimentary tract, kidneys, liver, spleen, etc., which may be attributed to the fact that all the patients in our series had profound neutropenia due to cytotoxic chemotherapy for underlying hematologic malignancies.

The most likely portals of entry for *Trichosporon* are the gastrointestinal and respiratory tracts (9–11). The current histopathologic study of seven patients revealed *Trichosporon* invasion of the gastrointestinal mucosa and blood vessels. Fungal invasion of the lungs was seen predominantly in blood vessels, rather than in bronchioloalveolar spaces. These findings suggest that the alimentary tract is the more likely portal of entry in patients with hematologic malignancies. Cytotoxic anticancer drugs such as cytosine arabinoside may injure the mucosa of the alimentary tract. Moreover, broad-spectrum antibiotics can severely disrupt the normal microbiologic flora of the alimentary tract, allowing colonization and proliferation of *Trichosporon*. The fungi could then invade blood vessels through the disrupted mucosal barrier of the alimentary tract (32). Haupt et al. (21) observed that gastrointestinal colonization preceded the development of disseminated *Trichosporon* infection. Recently, Walsh et al. (25) observed that *Trichosporon* organisms advanced from the gastrointestinal tract to visceral tissue in persistently granulocytopenic rabbits. Thus, the alimentary tract is considered the major portal of entry in patients with hematologic malignancies. On the other hand, as also mentioned in their reports, chronic indwelling vascular catheters might be another potential portal of entry. This view is supported by the fact that all of the patients in our series had a central and/or peripheral venous catheter.

Infection-related mortality of disseminated *Trichosporon beigelii* infection in Japan is 88 %. The high mortality of trichosporonosis, despite the aggressive use of amphotericin B, may be related to the resistance of *Trichosporon* to the fungicidal effects of amphotericin B (33). On the basis of their experimental and clinical results, Anaissie et al. (34) concluded that antifungal azoles represent effective therapy for infection with *Trichosporon*. Of five survivors in Japan, two received amphotericin B in combination with 5-flucytosine, one amphotericin B with miconazole and two miconazole alone. However, the resolution of infection in leukemic patients with neutropenia seems to be related primarily to bone marrow recovery following remission of leukemia. Therefore, administration of granulocyte/macrophage-colony stimulating factor (GM-CSF) or G-CSF should be considered, despite the drawback of increasing the leucocyte count and the probable stimulatory effects of these cytokines on residual Philadelphia-positive clones.

Disseminated *Trichosporon beigelii* infection is an emerging fatal opportunistic infection. We believe the immunohistochemical method, which can be applied to biopsy specimens, is a useful tool for diagnosis. Further investigations are needed to elucidate the pathogenesis of trichosporonosis and to determine the most effective antifungal therapy for this disease.

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