Case report

Generalized lymphadenopathy caused by *Trichosporon asahii* in a patient with Job’s syndrome

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Of the six species of *Trichosporon* known to cause human infections, *T. asahii* is the main agent of invasive trichosporonosis. We describe an unusual case of generalized lymphadenopathy due to *T. asahii* in a 10-year-old boy with Job’s syndrome (markedly elevated IgE with eosinophilia). The diagnosis was based on the presence of blastic conidia and hyphal elements breaking into arthroconidia in biopsied tissue of the cervical lymph node and isolation of the causal agent *T. asahii* in pure culture. The patient responded initially to amphotericin B therapy, but the infection recurred within 4 weeks and did not respond to therapy of liposomal amphotericin B and 5-fluorocytosine for 10 days. The patient left the hospital against medical advice.

**Keywords** generalized lymphadenopathy, hypereosinophilia, Job’s syndrome, trichosporonosis, *Trichosporon asahii*

Introduction

Hypergammaglobulinemia and recurrent infections are the characteristic features of the Job’s syndrome, which is a granulomatous disease variant. The disorder is rare and most often occurs sporadically. *Staphylococcus* spp. and *Candida* spp. are the usual etiological agents causing pneumonia and abscesses. Affected patients often demonstrate eosinophilia of varying degree and hyper-immunoglobulin E [1].

Six species of the genus *Trichosporon* Behrend are medically important, causing deep-seated, mucosa-associated and superficial infections. These species are: *T. asahii*, *T. asteroides*, *T. cutaneum*, *T. inkin*, *T. mucoides* and *T. ovoides* [2,3]. Clinical relevance of these six species was first reviewed by Guého et al. [3]. Based on sequences of the ribosomal internal transcribed spacers, Sugita et al. [4,5] confirmed the validity of these species. Guého et al. [6] considered *T. beigelii* as a name of doubtful identity and rejected it. According to their new revision [2,3,6], *T. asahii* is the principal etiological agent of systemic trichosporonosis, so that most of the isolates previously reported in the literature as *T. beigelii* and/or *T. cutaneum* from invasive deep infections would belong to *T. asahii*. The majority of invasive infections due to *T. asahii*, especially in immunocompromised patients, are fatal [7–9]. Patients with hematological malignancies often develop infection with *Trichosporon* spp., especially *T. asahii* [10–13]. Recently, *T. asahii* has been found to be a major agent of the seasonal and chronic type of hypersensitivity pneumonitis in Japan [14–16].

In this brief communication, we share our unique experience of managing a young child with Job’s syndrome who had generalized lymphadenopathy caused by the combination of *T. asahii* and hypereosinophilia.

Case report

A 10-year-old boy was referred to us with a history of progressively enlarging, generalized lymph nodal swel-
lings over the preceding 4 months. There was no history of fever, bone pains, night sweats, loss of weight, skin bleeds or anorexia. There was no contact with infectious illnesses such as tuberculosis. There was no history of atopy and no skin manifestations were observed. Examination revealed a well-nourished and well-built child with nontender, nonmatted, firm lymph node swellings (1.5–3.0 cm in diameter) in cervical, axillary and inguinal regions. Apart from lymphadenopathy, there were no other abnormal findings. Blood count revealed: hemoglobin 10.7 g dl⁻¹; white blood cells 27.5 × 10³ l⁻¹; differential leukocyte count P₃L₅ EⱧ₂; absolute eosinophil count 15.95 × 10² l⁻¹; platelet count 223 × 10⁹ l⁻¹; erythrocyte sedimentation rate 30 mm fall in the first hour. Blood biochemistry, including serum electrolytes, blood urea nitrogen, serum creatinine, serum calcium and inorganic phosphate, serum magnesium and liver function tests, was within normal limits. Aerobic and fungal cultures were sterile. Fungal serology for antibody against *Candida albicans* and *Aspergillus fumigatus*, *A. flavus* and *A. niger* by gel diffusion test was negative. Latex-agglutination test for capsular antigen was negative for *Cryptococcus neoformans*. X-Ray of the chest showed right hilar lymphadenopathy. The tuberculin test with one tuberculin unit was negative. Ultrasonographic examination of the abdomen revealed multiple, retroperitoneal lymph nodes.

Fine-needle aspiration cytology from axillary and cervical lymph nodes showed a polymorphic population of cells composed of reactive lymphoid cells with many eosinophils. Many multinucleated giant cells were seen. No fungi or parasites could be demonstrated on special stains. A cervical lymph node biopsy was then performed. There was partial effacement of the nodal architecture by hyalinized nodules. The paracortical areas showed diffuse infiltration by many eosinophils. There were Langerhans and foreign-body giant cells that contained oval budding cells of fungal etiology. In addition to budding yeast cells, many hyphal fragments breaking into arthroconidia were observed, suggesting *Trichosporon* spp. (Fig. 1).

The lymph node biopsy sample was cultured on Sabouraud glucose agar containing chloramphenicol (Sab + C) and Sab + C containing cycloheximide (Sab + C+C). Cultures were incubated in the dark at 25 and 37 °C. Several white, yeast-like colonies were observed after 48–72 h of incubation. When the fungus was grown on cornmeal Tween 80 agar, many budding cells, true hyphae and hyphae breaking into arthroconidia were observed. Carbon assimilation profiles were studied using the API 20C AUX system (Bio Mérieux, Marcy l’Étoile, France). Following 48- and 72-h incubation, based on assimilation profiles 274 4730 and 274 4770, the isolate was identified as *T. asahii*. The minimum inhibitory concentration (MIC) of the isolated strain was determined by reference method for broth dilution antifungal susceptibility testing of yeasts (National Committee of Clinical Laboratory Standards, USA) [17]. The MIC against amphotericin B (Hi Media, Mumbai, India) was 4 μg ml⁻¹, 5-fluorocytosine (Sigma, St. Louis, MO, USA) 8 μg ml⁻¹, fluconazole (FDC, Mumbai, India) 16 μg ml⁻¹, ketoconazole (Torrent Laboratories, Ahmedabad, India) 2 μg ml⁻¹, itraconazole (Janssen, Beerse, Belgium) 0.25 μg ml⁻¹.

The documentation of a deep *T. asahii* infection prompted a detailed assessment of the patient’s immune system. Serum electrophoresis revealed a mild hypergammaglobulinemia. The IgE level was 22,837 IU ml⁻¹ (normal = 1.4–300 IU ml⁻¹). The skin test reaction to Candidin (Hollister Stier, Spokane, WA, USA) was negative. The nitroblue tetrazolium test and phytohaemagglutinin activation were normal. CD3 and CD19 cell counts were within normal limits. ELISA tests for human immunodeficiency virus (HIV) 1 and 2 were negative.

The patient was treated with oral itraconazole (10 mg kg⁻¹ day⁻¹) for 28 days. No change in the size of lymph nodes was observed at the end of this therapy. He was then treated with intravenous infusions of amphotericin B in a cumulative dose of 26 mg kg⁻¹ over a period of 4 weeks. Serum electrolytes, liver and renal function tests were regularly monitored and remained within normal limits. At the end of therapy, the lymph nodes had regressed to less than a fifth of their original size while the absolute eosinophil count had decreased to 1.4 × 10⁹ l⁻¹.

After an interval of 4 weeks, the child returned with
progressive enlargement of the lymph nodes. Aspiration cytology from the lymph nodes again demonstrated the presence of yeast-like fungal bodies and on culture *T. asahii* was again isolated in culture. Liposomal amphotericin B (cumulative dose of 30 mg kg\(^{-1}\) over a period of 10 days) and oral flucytosine (5 mg kg\(^{-1}\) for 10 days) were administered. No significant change in the size of the nodes was observed. The parents got a discharge of the patient on request and did not return for further evaluation.

**Discussion**

Invasive infections caused by *T. asahii* have been reported in immunocompromised individuals. The majority of these infections have been documented in patients with acute leukemia and severe neutropenia. Fever, pneumonia and/or skin rash were major clinical manifestations [7–10]. According to the recent revision of *Trichosporon* [2,3], *T. asahii* is the predominant species regularly involved in systemic infections especially in immunocompromised and neutropenic patients. Our patient had nonregressing generalized lymphadenopathy. He had no other recurrent infections. The generalized lymphadenopathy caused by *T. asahii* prompted a search of immunodeficiency. The markedly elevated IgE levels and the hypereosinophilia were manifestations consistent with the diagnosis of Job’s syndrome. As far as we are aware, invasive infection by *T. asahii* in Job’s syndrome has not been reported previously. Similarly generalized lymphadenopathy has not been described in association with *Trichosporon* infections.

Even after Guého et al.’s taxonomic revision of the genus *Trichosporon* and rejection of *T. beigelii* as a doubtful species in 1992 [2,6], several reports describing cases of septicemia [18–22], pneumonia [23], chronic meningitis [24], endocarditis [25,26], invasive infections in neutropenic patients [12,23,27] and transplant recipients [28], catheter-related infections in surgical patients [29,30], and blood stream infection in a burn patient [31] have identified the causal agents under the rejected binomial *T. beigelii*. In several reports prior to Guého et al.’s revision, causal agents of systemic, invasive trichosporonosis were identified as *T. beigelii* or *T. cutaneum* [32–34] or these two species names were used interchangeably [35]. A re-examination of these isolates is necessary to determine their specific identity.

The partial response to therapy with amphotericin B and the subsequent exacerbation in the size of lymph nodes in the present case reflects *Trichosporon*’s known resistance to conventional antifungal agents. Many *Trichosporon* spp. are known to be resistant to 5-fluorocytosine, while our strain was intermediate. Keay et al. [36] also reported similar results. Among seven strains they tested against amphotericin B, they found MICs varying between 2 and 4 µg ml\(^{-1}\). However, Guého et al. [3] found amphotericin B MICs to be much lower than those reported by Keay et al. Even when there is established in vitro sensitivity to amphotericin B, ketoconazole and itraconazole, clinical *Trichosporon* infections often show a poor prognosis. Walsh et al. [37] found minimum lethal amphotericin B concentrations against *T. beigelii* to be considerably higher than MICs. Generally, successful cure is often associated with recovery from granulocytopenia. Anaissie et al. [38] recently reported seven of their patients with *T. beigelii* infections responding to azole derivatives (fluconazole, miconazole and SCH39304). Six of those patients were immunocompromised and four were neutropenic. Though our strain had an MIC (0.25 µg ml\(^{-1}\)) in susceptible, dose-dependent range against itraconazole, it did not respond to 28 days’ therapy. Preliminary in vitro and in vivo studies suggest that interferon gamma therapy may be beneficial in Job’s syndrome [39,40]; however, we were unable to employ this strategy. This case highlights the recent emergence of *T. asahii* and the need to develop antifungal treatments suitable for such patients.

**References**


