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Allogeneic Hematopoietic Stem Cell Transplantation Combined with Disseminated Infection by Trichosporon Asahii: A Case Study and Literature Review

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1. Abstract

Invasive fungal disease (IFD) is a common postoperative complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT), the most common bacterial pathogen being Candida and Aspergillus. In recent years, the incidence of rare yeast infections, which is difficult to treat and has a high mortality, has gradually increased. Here we report the diagnosis and treatment process of allo-HSCT combined with Disseminated infection by Trichosporon asahii from our hospital and review some of the references.

2. Medical Records

The patient was a 26 years old male with a medical history of 3 years and 9 months. Onset with "fatigue" and leukocytes number being 15×10^9/L, he was diagnosed as "acute myeloid leukemia-M6". HLA-identical sibling allogeneic hematopoietic stem cell transplantation was performed under second complete remission status. Pretreatment was a modified Bu/Cy regimen, and graft-versus-host disease (GVHD) prevention was performed with cyclosporine + Mycophenolate + short-course methotrexate. Total MNC was 7.2×10^8/kg and CD34+ was 4×10^6/kg. The treatment of posaconazole was maintained during the transplantation as it was effective in preventing lung infection. The blood drug concentration is maintained at 0.5-1.0 ug/ml.

On day 6 post-transplantation (+6 days), the patient experienced left shoulder pain, limited movement of the left upper extremity and upward lifting. Physical examination reported swelling skin tissue at the painful site with unclear boundary, normal temperature, softness, mild tenderness, and no subcutaneous nodules. Vascular ultrasonography showed irregular hypoecholic areas of 2.4×0.3 cm, 0.8 × 0.2 cm in the proximal section of the Vena basilica and in the axillary vein, respectively. Thrombosis cannot be excluded, the affected limb was immobilized, and peripheral blood + PICC blood was cultured to exclude skin and soft tissue infections. The highest body temperature of the patient reached 38.6 °C on +8 days, and the ache in the left upper extremity was aggravated to the wrist joint, accompanied by symptoms of frequent and urgent micturition, urodynia, and bladder irritation. Multiple patchy ulcers of the penis were reported on physical examination, along with multiple painful nodules on the left upper extremities near the shoulders, elbow sockets, and testicles. Test showed NET 0×10^9/L, CRP 114 mg/L, PCT 0.7 ng/ml, G test 104 pg/ml, urine BKV 2.0×10^8 copies/ml. Ultrasonography shows that the irregular low echo area of the near-heart segment of the Vena basilica is 2.7×0.3 cm, the local muscular tissue at the pain site of the left upper extremity is thickened by about 0.91 cm, the internal echo is unevenly reduced, the muscle layer near the shoulder of the left upper limb and the muscle layer near the elbow fossa of the left upper limb showed low echo area with a clear boundary, and the size of the sites are 1.6×0.8cm, 1.8 × 1.0 cm, respectively. Inflammatory lesions are not excluded. +6 days' blood culture was negative, but +8 days' blood culture (Figures 1 and 2), urine culture, penile secretion culture, and serum NGS all indicate Trichosporon asahii infection.

Clinically diagnosed as "disseminated Trichosporon asahii infection (fungemia, skin)". Bilateral PICC was removed immediately, antifungal therapy with voriconazole was used instead, the blood concentration was maintained at 1.5-2.5 ug/ml, berberine combined with amphotericin B local wet compresses were given after ethanol disinfection, and G-CSF promoted neutrophil grafting. On +13 days, the patient's body temperature returned to normal, the pain in the left limb decreased, the ulcer wound was reduced, and the painful nodules near the shoulder and elbow fossa and testicles of the left upper limb were reduced. Cardiac ultrasonography and brain CT examination did not show abnormalities. CT shows new nodular high-density shadows in both lungs, and small nodular low-density shadows in the liver, spleen, and kidneys. No significant strengthening is seen after enhancement, and infectious lesions are considered. The diagnosis was revised to "disseminated Trichosporon asahii infection (fungemia, skin, lungs, liver, spleen, and kidneys)". Peripheral blood culture was negative from +20 days' samples, but Trichosporon asahii growth was observed in urine culture. Additional amphotericin B 25 mg/day treatment was applied on +20 days, and urine culture was negative on samples from +29 days. Re-examination of CT on +60 days showed that the lungs, liver, spleen, and kidneys had multiple small nodular-like low-density opacities and reductions. Decreased vision in the right eye and visual field defects were reported on +84 days, but the vision in the left eye remained normal. Physical examination showed light perception in the right eye, 0.5 in the left eye, and intraocular pressure of 10 mmHg. Submacular and fundus retinal hemorrhages were seen in the dilated fundus, and irregular infectious lesions on the temporal side of the macula (Figures 3 and 4). T. asahii was detected by NGS in aqueous humor. The diagnosis was revised again to "Disseminated Trichosporon asahii infection (fungemia, skin, lungs, liver, spleen and kidneys, eyes)". Oral voriconazole combined with intravitreal injection of voriconazole and amphotericin B, and the fundus hemorrhagic lesions improved after 6 times of treatments. Six months after transplantation, a series of operations were performed on the right eye, including reattachment operation of retinal detachment with periretinal membrane, transconjunctival micro-invasive vitrectomy, vitreous cavity puncture, and panretinal laser photocoagulation, during the which the serum and aqueous humor concentrations were maintained at 1.5-2.5ug/ml.

At present, 10 months after hematopoietic stem cell transplantation, the patient's primary disease continued to remission. No active infection of T. asahii was detected, and oral voriconazole antifungal therapy was continued.

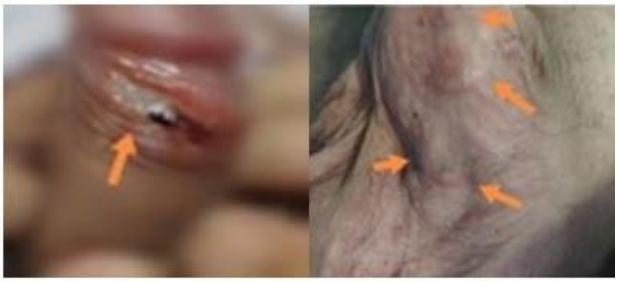

Figure 1: Perineal skin ulcers and nodules +8 days after HSCT

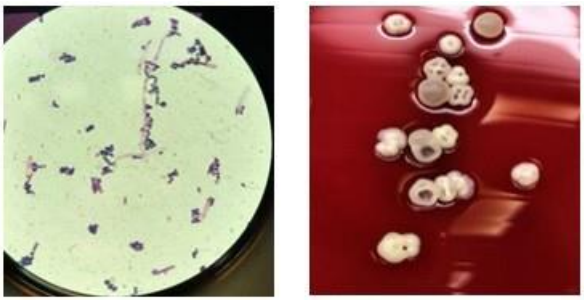

Figure 2: Blood smear and culture at +8 days after HSCT
A. Blood smear: slub-like arrangement of strains;
B. Medium: Candida gyrus-like colonies

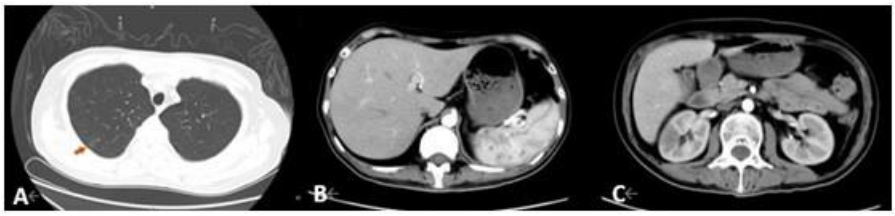

Figure 3: Lung and abdominal CT scans + 20 days after HSCT

A. Lung CT: multiple small nodular high-density shadows can be seen in both lungs, and there is a high possibility of infectious lesions (fungi-monadium);

B+C. Abdominal CT: The volume of liver and spleen increased, multiple small nodular low-density shadows were seen in it, and small nodular and mass-like low-density shadows were seen in both kidneys; no obvious enhancement was seen after enhancement;

A. +84 days after HSCT: submacular hemorrhage, fundus retinal hemorrhage;

B. +114 days after HSCT: submacular hemorrhage, retinal yellow-white lesions;

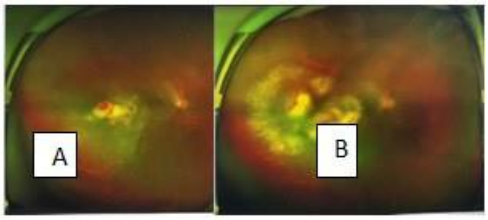

Figure 4: Mydriatic fundus of right eye

A. +84 days after HSCT: submacular hemorrhage, fundus retinal hemorrhage;

B. +114 days after HSCT: submacular hemorrhage, retinal yellow-white lesions;

3. Case Discussion and Literature Review

Trichosporon asahii is a yeast-like opportunistic fungus that causes agranulocytosis or immunodeficiency, exposure to broad-spectrum antibiotics or steroid hormones, implantation of invasive medical devices, and inappropriate use of antifungal drugs. The most common cause of severe invasive Trichosporon spp infections, accounting for approximately 68%-90%. Up to 80% of the patients suffer catheter-associated fungemia, and the mortality rate is 40%-90% [1-6]. T. asahii can form complex three-dimensional grid-like biofilms on the surface of implanted devices, and the ERG11 gene can reduce azole affinity, which is the cause of its high drug resistance and mortality. Containing the underlying diseases and sources of infection, resection of implanted devices, recovery of granulocytes, and voriconazole treatment can improve prognosis [1-3,6-8]. The patient in this article was diagnosed with acute myeloid leukemia. At the time of onset, the patient was in the process of allogeneic stem cell transplantation for hematopoiesis, and the immune system has not yet been rebuilt. He has almost all high-risk factors for the occurrence of T. asahii infection. The clinical manifestations include fungemia, and multiple organs such as skin, lung, liver, spleen, kidneys, and eyes are involved, similar to those reported in the literature [1-8]. This is the patient with the most organs involved at the same time in the reports related to T. asahii infection, suggesting that we should conduct multi-organ screening for systemic disseminated infection in a timely manner when fungemia occurs.

The early papers reported that strains were found in the corridor air, laminar flow bed, equipment clean room, washbasin, and patient pollutants of hematology wards with disseminated infection of T. asahii, suggesting the possibility of cross-infection [9-11]. However, a recent study in Japan found that the colonization rate of T. asahii in the feces of healthy subjects was 60%, and the genotype was almost the same as that of the clinically reported isolates, the authors also speculate that early colonization of the gastrointestinal tract by the strain may be associated with the late-stage development of trichosporidiosis [6]. Kurakado et al. isolated 4 strains in 5 patients with COVID-19 combined with T. asahii infection, which reduced the possibility of infection transmission [1]. Most of the predominant molecular genotypes of T. asahii are type 1, followed by types 3 and 5, but there is no significant relationship between strain genotypes and virulence, antifungal drug susceptibility, and clinical prognosis [2,12-15]. In the 2021 edition of the Global Guidelines for the Diagnosis and Management of Rare Yeast Infections, voriconazole or posaconazole are recommended as first-line drugs because of their highest antibacterial activity, followed by fluconazole which shows moderate sensitivity. Amphotericin B exhibits variable minimum inhibitory concentrations (MICs) and is recommended for second-line therapy. The guideline does not recommend it due to the natural resistance of T. asahii to echinocandins [1-5,13-16]. Since serum concentrations of antimicrobials have not been mentioned in previously reported cases, it remains unclear whether they play an important role in the development of breakthrough infections. In this study, the disseminated T. asahii infection was not contained even when the blood concentration of

posaconazole reached the standard preventive dose (≥0.7ug/ml), while the treatment with voriconazole was effective. This implies that the latter has a higher affinity to fungal 14-α - demethylases, while inhibiting the demethylation of 24-methylenedihydrolanosterol in yeast and filamentous fungi. it can inhibit the demethylation of 24-methylenedihydrolanosterol in yeast and filamentous fungi, and thus achieve the purpose of treatment. It is speculated that patients with immunocompromised patients are more dependent on the bactericidal activity of fungal drugs. Considering that voriconazole is not metabolized by the kidneys, while amphotericin B has the Pharmacokinetic characteristics of hypermetabolism in the kidneys, we tried the combined drug when the patient had a urinary tract infection. The effect was remarkable. In addition, the onset of fungal endophthalmitis is insidious, the treatment cycle is long and difficult, and it is likely to leave permanent organ functional damage. During the anti-infection process, the fundus should be regularly monitored. Finally, ethanol disinfection can effectively inhibit the biofilm formation of T. asahii [8], and the combined use of berberine and amphotericin B has a synergistic destruction effect on planktonic cells and biofilms of T. asahii [17] and achieved good results in the care of patients with skin ulcers.

In conclusion, disseminated T. Asahii infection is a rare yeast infection that involves multiple organs. Early detection, early diagnosis and treatment, and combined medication can improve the prognosis.

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