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Case Report

Disseminated fusariosis emerged from prolonged local genital infection after cord blood transplantation

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ABSTRACT

Disseminated fusariosis (DF) is a rare life threatening fungal infection in immunocompromised hosts. We herein report a case of a fatal DF mimicking varicella zoster virus (VZV) infection that was emerged from a localized genital infection during cord blood transplantation (CBT) in a patient with severe aplastic anemia (SAA). The patient developed an ulcer following small painful vesicles mimics herpes simplex virus infection (HSV) on the glans penis before CBT, but a *Fusarium* species was identified. Despite administration of voriconazole, liposomal amphotericin B and granulocyte transfusion, the lesion was extended to extensive skin looked like VZV infection and the patients died after CBT. Massive fusarium infiltration was detected in multiple organs at autopsy. A genetic analysis of the mold identified *Fusarium solani* after his death. It should be noted that in patients with fusarium infection, localized and disseminated lesions of fusarium infection sometimes mimic HSV and VZV infections, which hampers an early diagnosis.

1. Introduction

Fusarium is a ubiquitous fungus that is widely distributed in soil and plants. While fusarium species cause superficial cutaneous infections with a good prognosis in immunocompetent hosts, they may cause invasive and disseminated infections in immunocompromised hosts, with a mortality rate as high as 40–80% [1–6]. We herein report a case of a fatal disseminated fusariosis (DF) mimicking disseminated varicella zoster virus (VZV) infection following a localized genital infection mimicking genital herpes simplex virus infection (HSV) during cord blood transplantation (CBT) in a patient with severe aplastic anemia (SAA).

2. Case report

A 44-year-old man was diagnosed as SAA in January 2012. He only showed a transient response to immunosuppressive therapy with cyclosporine and corticosteroids, in combination with granulocyte colony stimulating factor (G-CSF). He was then referred to our institute to undergo CBT in March 2012, six months before transplantation. He developed fungal pneumonia. A sputum culture and bronchoalveolar lavage fluid culture was performed, which did not detected fungus. We diagnosed probable invasive fungal infection due to the elevation plasma level of ß-D-glucan (BDG) and the nodular pulmonary lesion. The pneumonia was successfully treated with oral voriconazole (VRCZ) (400mg/day) followed by liposomal amphotericin B (L-AMB) (2.5 mg/kg). At 10 weeks before CBT, an abdominal wall abscess was developed, we performed puncture of abscess, but no pathogens were detected. Abscess was

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cured after empirical treatment with levofloxacin, sulfamethoxazole/trimethoprim, and oral VRCZ (400 mg/day) for one month. At seven weeks before CBT, he developed small painful vesicular lesions on the glans penis. The vesicles merged and formed an ulcer after a few weeks (Fig. 1). The ulcer developed from vesicular lesions on the glans penis was strongly suspected to be genital HSV infection by a dermatologist based on a visual inspection and the clinical course. The patient was treated with Ara-A ointment in vain. Thus, a cultivation survey of a skin scraping from the ulcerative lesion on the glans penis was performed on day -10 of CBT (day -10). Acyclovir (1000 mg/day), sulfamethoxazole/trimethoprim, meropenem, and intravenous VRCZ (400 mg/day) started from day -7 to prevent HSV/VZV, *Pneumocystis jirovecii*, and fungal infections, respectively. The patient had infections repeatedly due to persisted neutropenia; therefore, we decided to perform CBT in order to recovering neutropenia. Prophylactic granulocyte transfusion (GTx) was also performed on days −14, −13, −7 and −6 to prevent bacterial and fungal infections. The conditioning regimen (fludarabine, melpharan and total body irradiation) was administered from day −6. The culture grew a white fluffy filamentous fungus on day −3, which was identified as a *Fusarium* species based on the morphological characteristics. The patient received 2.34×10^7/kg cord blood nucleated cells. On day +1 after CBT (day +1), he developed a high fever and disseminated small vesicles on his trunk and extremities, mimicking disseminated VZV infection. The dose of acyclovir was increased to 1500 mg/day on day +1. From the elevation of plasma level of BDG to 74.2 pg/mL, we determined that VRCZ was not effective. VRCZ was replaced by L-AMB (5.0 mg/kg) on day +4. Blood cultures were performed on day −2, +5 and +6. One of these blood cultures obtained on day +6 detected molds 72 hours later. Although additional GTx was performed on days +7 and +8, the patient developed septic shock and died on day +10. A postmortem examination revealed a number of small nodular lesions (5–10 mm) throughout the patient's body. The sites included the skin (Fig. 1), penis, lung, heart, spleen, kidney, laryngopharynx, esophagus, stomach, small intestine, colon, mesentery, pancreas, thyroid, and left adrenal gland. A histological examination of these lesions demonstrated that the nodules consisted of molds that were found to invade the blood vessels in each lesion (Fig. 1). There were no findings of bacterial or viral infection. The molds grown from skin culture obtained on day −10 were subjected to a *Fusarium*- and *Fusarium solani* species complex (FSSC)-specific real-time polymerase chain reaction (PCR) [7] and the sequencing of translation elongation factor 1 (EF1-α) and the nuclear ribosomal internal transcribed spacer (ITS) region. Based on the findings, *Fusarium solani* (*F. solani*) was identified after his death. Antifungal susceptibility testing also revealed that it was resistant to VRCZ and that it was only susceptible to amphotericin B (Table 1) after his death.

3. Discussion

Fusarium is a ubiquitous fungus in soil, plants, and air [8,9]. Although *Fusarium* species have long been recognized as etiologic agents of localized superficial infections in immunocompetent hosts, they have come to be recognized as causative agents of disseminated mold infection in immunocompromised hosts, such as hematopoietic stem cell transplantation recipients and patients with SAA [10].

The disruption of skin and mucosal barriers by direct trauma potentiate local fusarium infections in non-immunosuppressed patients. Patients with local fusarium infection often presents with ocular, nail and cutaneous lesions, including granulomas, ulcers, nodules, mycetomas, necrosis, panniculitis, intertrigo and vesicles [9,11]. On the other hand, the airway, skin and intestinal tract have been reported as entry sites of DF [3,12,13]. Among an immunocompromised hosts, fusarium infection presents skin involvement (72%) [1], fungemia (41%) and pneumonia (39%) [14]. In an immunocompromised host, localized fusarium infection tends to become subsequent DF [2]. DF presents as persistent fever and myalgia with sinusitis, endophthalmitis, pneumonia, myositis and central nervous system infection, and the most frequent pattern of DF is a combination of skin involvement and fungemia, with or without other involvement [14]. It often causes hemorrhage, thrombosis and tissue necrosis of various organs, because *Fusarium* species show a tendency toward vascular invasion, similar to aspergillus species [15]. The direct cause of death in our patient

Table 1
The minimal inhibitory concentrations (MICs) and minimal effective concentration (MEC) of antifungal agents against Fusarium solani.

	Endpoint	MIC/MEC
MCFG	MEC	>16
AMPH-B	MIC100	1
5FC	MIC50	>64
FLCZ	MIC50	>64
ITCZ	MIC100	>8
VRCZ	MIC100	>8
MCZ	MIC50	8

MCFG, micafungin; AMPH-B, amphotericin B; 5FC, 5-fluorocytosine; FLCZ, fluconazole; ITCZ, itraconazole; VRCZ, voriconazole; MCZ, miconazole.

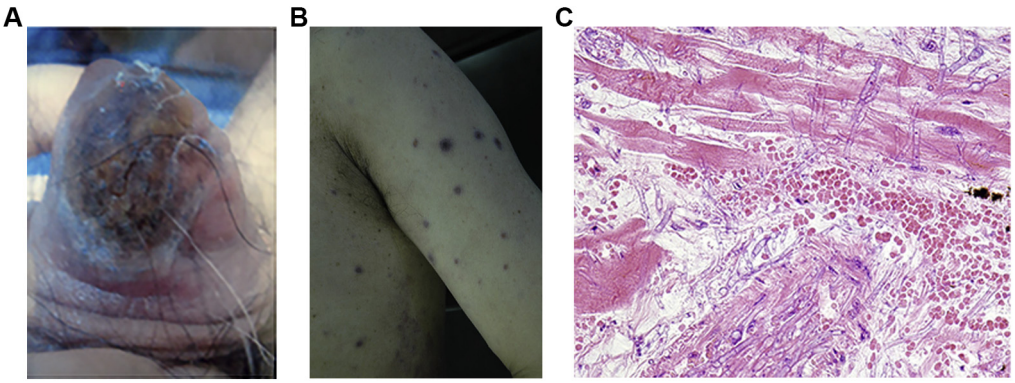

Fig. 1. Clinical images of Fusarium infection in our case. The skin ulcer on the glans penis that developed after the following vesicle lesion mimicking herpes simplex virus infection are shown. (A) Vesicular lesions mimicking disseminated varicella zoster virus infection at autopsy. (B) A microscopic examination demonstrated the invasion of mold in the vessels and heart muscles. (C).

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