A disseminated filamentous fungal infection that broke through echinocandin antifungal treatment

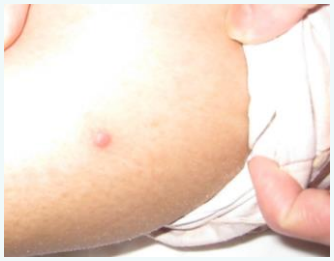
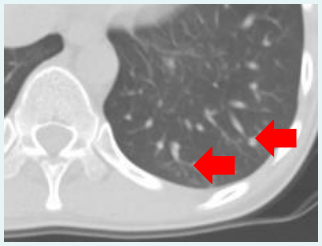


Photo 1: Rash on left thigh



CT 1: Disseminated lesions of left lung

Case history 1

34-year-old female, 15 days after allogeneic hematopoietic stem cell transplant for acute myelogenous leukemia. Her white blood cell count had been <100/μL for about 20 days and was expected to begin recovering soon.

She had been treated with carbapenems, glycopeptides, and candin antifungals for over ten days for a persistent fever, and had received acyclovir as prophylaxis. Painful skin rashes appeared on the right ankle, knees, left thigh, and right armpit 4.5 days ago. (See photo 1, left)

Vital signs and laboratory findings 1

Temperature 39.6C, blood pressure 104/58, heart rate 118 bpm, respiratory rate 16, and O2 saturation 98%.
Slight discomfort in right costal region. Mild redness and tenderness around anus (signs of improvement observed).
No other significant symptoms or physical abnormalities observed.
WBC 100/μL, Hgb 11.8 g/dL, Plt 39,000/μL, T-Bil 0.7 g/dL,
GOT 17 IU/L, GPT 57 IU/L, LDH 86 IU/L, ALP 406 IU/L
Beta-d-glucan 10.5pg/ml <20, Aspergillus GM antigen negative
Blood culture, skin biopsy, and whole body CT scan performed.
Disseminated lesion in lung field (CT 1), biopsy revealed filamentous fungus (Photo 2)
Tissue culture identified *Fusarium oxysporum*, blood culture was negative

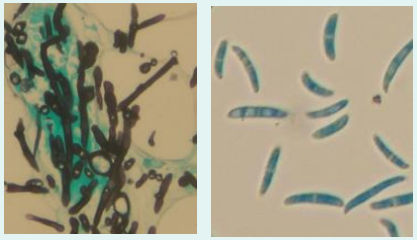


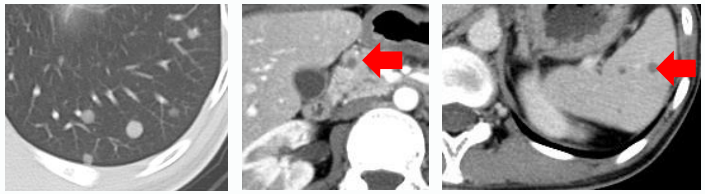
Photo 2: Skin biopsy
Left (Grocott stain): Acute-angle branching septate hyphae
Right (Culture result): Crescent-shaped conidia

Clinical course 2

Skin rash disappeared after antifungal drug was changed to voriconazole. Eighteen days post-transplant, blood cell count started recovering and fever subsided.
Prednisolone 1mg/kg started for graft versus host disease (GvHD).
Fever returned and skin rash appeared on extremities 29 days post-transplant.

Vital signs and laboratory findings 2

Tapping pain in right costal region, left abdomen and back
WBC 8300/μL, T-Bil 0.3 g/dL, GOT 28 IU/L, GPT 87 IU/L, LDH 153 IU/L, ALP 518 IU/L ,Beta-d-glucan 85.1 pg/ml, Aspergillus GM antigen negative
Skin biopsy detected same filamentous fungi in an initial test, all cultures negative
Fusarium susceptibility profiles: Amphotericin B 2mg/L, Voriconazole 8 mg/L
Voriconazole plasma concentration: 0.53 μg/mL < 1.0
Disseminated lesions in lung, pancreatic head, spleen, and kidney (CT 2).



CT 2: Disseminated lesions of lung, pancreatic head, and spleen

Clinical course 3

Her condition improved with early discontinuation of steroids, increased voriconazole dose, and the addition of liposomal Amphotericin B. It was thought that disseminated lesions might have become apparent during the neutrophil recovery period. She had chronic GVHD and received long-term prophylaxis (voriconazole) as secondary prevention after completion of treatment.

In case of antimicrobial treatment not being successful

Even under immunocompromised conditions such as severe neutropenia, antimicrobial therapy should be modified based on assumptions about the causative microorganism and infected organ.
In this case, if antifungals had been added or switched without a biopsy of the skin lesion during the neutropenic phase, it would be difficult to confirm the diagnosis of disseminated fusariosis.
It's very important to make every effort to diagnose causative microorganisms and infected organs.

Fusariosis:

Unlike Aspergillus, the most common filamentous IFI, candin antifungals are ineffective for fusariosis.
Appropriate treatment requires a definitive diagnosis.
Histological (morphological) differentiation from Aspergillus is difficult and beta-d-glucan and Aspergillus GM antigen can be positive, so **culture tests are important for definitive diagnosis.**
If treatment with antimicrobial treatment fails, it is important to investigate the cause.

Examples of items to confirm

- Complication of new infectious diseases or misdiagnosis of infectious disease
  - Check the spectrum of antimicrobial agents currently being administered
  - Infections with few symptoms (e.g., catheter infection, cholangitis)
- Incorrect antimicrobial dosage or administration
  - Confirmation of appropriate dosage, administration method and blood concentration
- Infections that require surgical intervention
  - Abscesses, foreign bodies, necrotic foci, etc.
- Cases where it may take more time to improve even with appropriate treatment
  - Abscesses, intravascular infections, osteomyelitis, severe immunodeficiencies, etc.
  - Transient clinical exacerbation, such as infections during neutrophil recovery or initial exacerbation at the start of treatment
- Non-infectious diseases
  - Drug fever, neoplastic fever, aspiration, heart failure, etc.

This case study was compiled at the request of AMR Alliance Japan as part of a series of case studies designed to show actual cases in which antimicrobials were and were not used as examples of antimicrobial stewardship.
The patient consent has been obtained for the publication of this case.
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