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# Fulminant candidemia diagnosed by prompt detection of pseudohyphae in a peripheral blood smear

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Short title: Candidemia in a peripheral blood smear

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**Abstract**

A 77-year-old man treated with prednisolone for pemphigus developed severe sepsis by *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus*. Several antibiotics were administered. A peripheral blood smear showed growth of a large number of yeast extending pseudohyphae which could be seen both inside and outside of leucocytes. Antifungal agents were added immediately, however, he did not recover. Several days later, blood culture showed *Candida albicans* septicemia. The autopsy revealed microabscesses in the lung, heart, liver and kidney. A large amount of neutrophil invasion and yeast with peudohypae were also detected.

## Background

The diagnosis of Candidemia is performed primarily by blood culture tests, it takes for several days to obtain the results. We report a rare case with candidemia in which the diagnosis was made rapidly by identification of numerous yeast with pseudohyphae and phagocytosis in the blood smear samples collected for the purpose of complete blood count.

**Case report**

A 77-year-old man was admitted to a nearby hospital for treatment of the bilateral leg skin blister. He was treated with 50 mg prednisolone per day for 4 months under a diagnosis of pemphigus, an autoimmune blistering disease. The eroded skin lesions were becoming ulcers with heavy exudates spreading to the whole body (Figure 1). Due to the damaged skin and mucous membrane barriers, the patient suffered from a severe bacterial infection, resulting in sepsis. Ceftazidime (CAZ) has been originally administered, but his systemic state did not improve.

Several months later, he was transferred to our hospital for treatment of an active and severe skin infection caused by multi-drug-resistant *Pseudomonas aeruginosa* (MDRP) and methicillin-resistant *Staphylococcus aureus* (MRSA). Physical examination on admission showed a fever of 38.0°C, loss of consciousness, sinus tachycardia (120 beats per min), tachypnoea (20 breaths per min), systemic edema, pleural effusion and ascites. Blood pressure was 120/60 mmHg. Laboratory data showed pancytopenia with a white cell count of $3.5\times10^{9}$/L (neutrophils 88%, lymphocytes 8%, monocytes 2%, metamyelocytes 1%, myelocytes 1%), anemia (hemoglobin 10.4 g/dl), thrombocytopenia (platelet count, $50.2\times10^{9}$/L), hypoproteinemia (total protein 4.4 g/dl, albumin 2.4 g/dl) and increased C-reactive protein (14.4 mg/dl). Conversely, the serum level of (1-3)-$\beta$-D-glucan was in the normal range (<5 pg/ml). The antibiotic administration was changed from CAZ to a combination of imipenem/cilastatin (IPM/CS), isepamicin (ISP) and teicoplanin (TEIC) due to the antibacterial sensitivity results. His general state improved temporarily, however, deteriorated after several days. Growth of a large number of yeast extending several pseudohyphae was detected on a blood smear collected in EDTA stained with May-Grünwald-Giemsa which could be seen both inside and outside of leucocytes (Figure 2a). Since it was suspected to be

*Candida species* morphologically, 400mg/day of fosfluconazole (F-FLCZ) was added immediately. It was documented that blood culture revealed *Candida albicans* septicemia three days later. The serum concentration of (1-3)- $\beta$ -D-glucan increased to 91.6 pg/ml. Yeast with pseudohyphae was persistently detected on peripheral blood smear examination. Despite additional administration of othet kind of antifungal drug, 150 mg/day of micafungin (MCFG), the patient died. The autopsy showed microabscesses of *Candida* species in the lung, heart, liver and kidney. A large amount of neutrophil invasion on a hematoxylin and eosin-stained sample and yeast with peudohypae on a Groccot-stained sample were also found in the tissues (Figure 2b).

## Discussion

Autoimmune blistering diseases are a group of disorders in which the body mistakenly attacks the tissue, causing blistering lesions that primarily affect the skin, mucous and membranes, systemic application of steroids is the first-line treatment. Previously, there is only one report of autoimmune blistering disease complicated with candidiasis [1]. Our case had many risk factors of candidemia existed such as serious extensive skin ulcer, with a long term glucocorticoid therapy and broad spectrum antibiotic agents therapy [2].

*Candida* species are dimorphic fungi with yeast or mycelial form. In the host organism, *C. albicans* usually has pathogenically a mycelial form which propagated rapidly in the blood and multiple organs [3]. Although pseudohyphae and true mycelia are typical of the parasitic adaptation of yeast, it matters whether they were obtained *in vivo* or *in vitro*. It was reported that *in vitro* phagocytosis of yeasts might occur by1-hour pre-incubation at 37°C [4]. However, the blood smear samples are prepared immediately after taking the patient's blood without incubation in our institute. Since the findings in autopsy of the patient validated the presence of pseudohyphae in infected tissues, we guessed that germination and the formation of pseudohyphae may have occurred *in vivo*.

Several reports have indicated that fungal elements may be detected in peripheral blood smears from patients suffering from severe intestinal disease or hematological malignancies or infant [5,6,7]. Because the pathogen is too small for visual detection, diagnosis of candidemia is rarely made by peripheral blood smears. In these reports, a large numbers of fungal elements existed. Detection of candidemia by blood smear requires at least $1 \times 10^5$ CFU/mL of yeast, which is clinically unusual; therefore, detection of candidemia by blood smear was supposed to be impossible in most cases

[8]. Septicemia is usually diagnosed by blood culture examination, however, the mean time required to positive yeast detection and to identify *C. albicans* were 35.3 h and 85.8 h, respectively [9].

In conclusion, careful observation of the peripheral blood smear may be useful for prompt diagnosis of candidemia. It is important for clinician to cooperate with laboratory staff to observe daily blood smear.

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**Figure legend**

Figure 1. Skin lesions of pemphigus, an autoimmune blistering disease, with erosions and ulcers with heavy exudates spreading over the whole body.

Figure 2. Yeast with pseudohyphae in *Candida albicans* (a) on a blood smear specimen stained with May-Grunwald-Giemsa and (b) on a Groccot-stained lung sample in autopsy.

Figure 1
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Figure 2a
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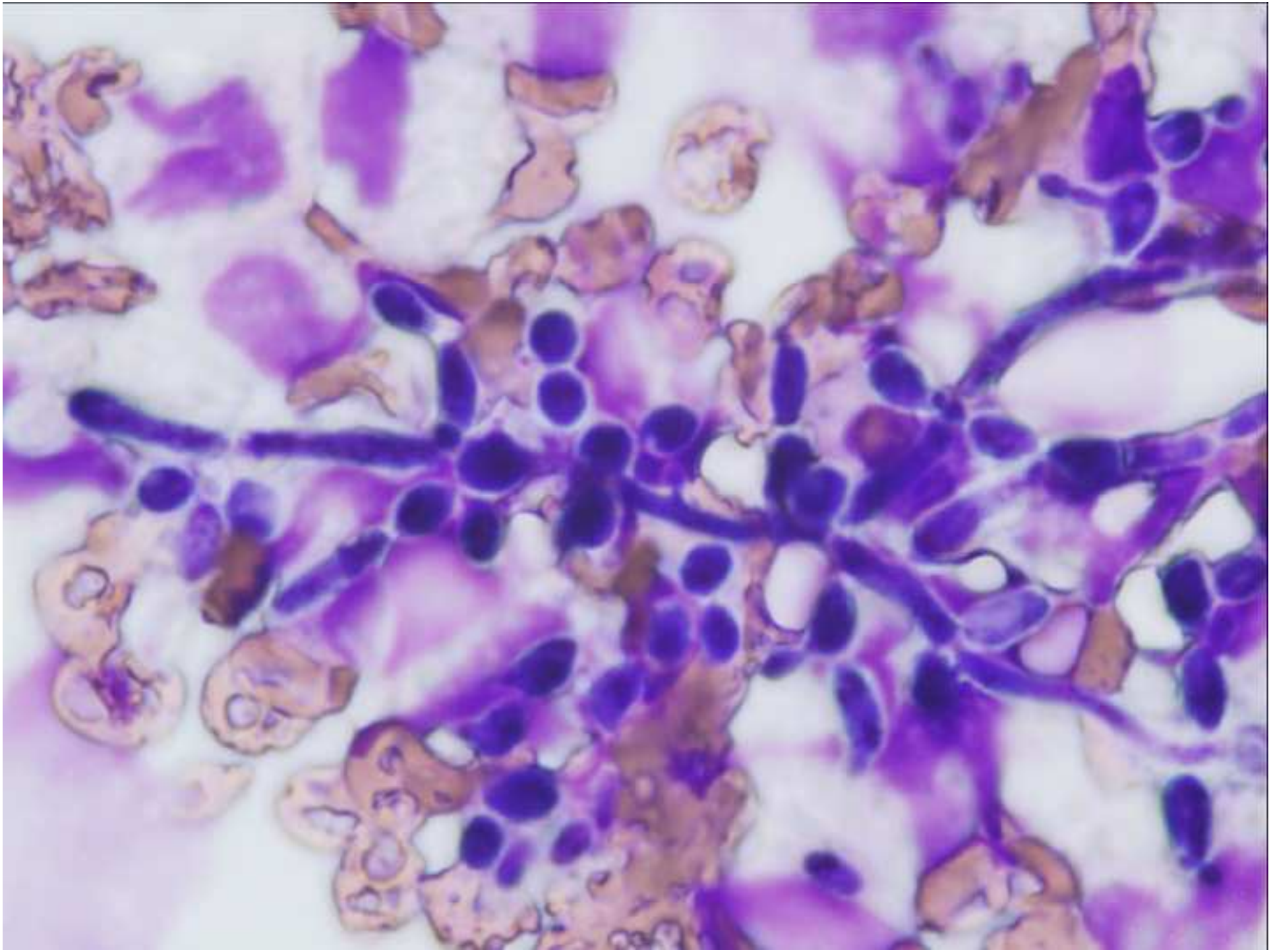

Figure 2b
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