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Early diagnosis of disseminated cryptococcosis by cryptococcal antigen lateral-flow assay

Dear Editor,

Disseminated cryptococcosis often develops in individuals with AIDS, chronic renal failure, transplant-related immunosuppression, and those taking high doses of drugs (corticosteroids and chemotherapy drugs) that suppress the function of the immune system.[1] Rapid diagnosis and effective combination therapy at an early stage for disseminated cryptococcosis is crucial for improving patient outcomes. According to the 2019 Revision and Update of the Consensus Definitions of Invasive Fungal Disease (EORTC) for defining cryptococcosis, cryptococcal antigen (CrAg) in blood or cerebrospinal fluid (CSF) confirms cryptococcosis.[2]

Owing to the increasing shift to point-of-care (POC) testing, several companies have manufactured POC tests for CrAg detection.[3] such as Dynamiker CrAg LFA (Dynamiker Biotechnology [Tianjin] Co., Ltd., China), a dipstick sandwich immunochromatographic assay for the detection of capsular polysaccharide antigens of *Cryptococcus* species complex in human serum and CSF.

A 33-year-old woman was presented with intermittent episodes of fever and headache for 2 months and painful erythematous plaques with oozing ulcers on the right lower leg. The leg lesions had persisted for 3 months and were aggravated in the last month (Fig. 1A), although ampicillin/sulbactam, piperacillin-tazobactam, and azithromycin were administered. She underwent renal transplantation due to renal failure eight years ago. Tacrolimus, mycophenolate mofetil, and methylprednisolone were administered until admission. The patient planted flowers in her private garden by using pigeon dropping for several years.

Physical examination at admission showed that her consciousness was alert, and her temperature was 37.4 °C. Laboratory findings showed normal peripheral white blood cell count and normal liver function, with the serum creatinine level of 122 μmol/L (reference value: 41.0–73.0 μmol/L). Serum β-D-glucan and galactomannan levels were normal (test values: 56.99 pg/mL and 0.14; reference values: >100 pg/mL and >0.5, respectively). However, the Dynamiker CrAg LFA was positive. Computed tomography (CT) of the lungs revealed a nodular lesion in the lingual segment of the left lung (Fig. 1B), and no abnormal findings observed in the head CT. Biopsy of the lesions over the right leg revealed many yeast cells (arrowheads) by Periodic acid–Schiff and Grocott's methenamine silver stain (Fig. 1C and D). The culture of the leg lesions tissue from biopsy yielded *C. neoformans*. Lumbar puncture revealed elevated opening pressure (220 mmH_2O), and studies of the cerebrospinal fluid showed high WBC (test value: 141 × 10^6/L, reference value: 0–8 × 10^6/L) count with 70% mononuclear cells and elevated protein (test value: 85 mg/dL, reference value: 15–45 mg/dL), as well as low glucose (test value: 2.18 mmol/L, reference value: 2.50–4.50 mmol/L) level. Further microbiological examinations of the CSF, including India ink stain and Dynamiker CrAg LFA, were found positive (Fig. 1E and F). Subsequent CSF culture yielded *C. neoformans*. Considering the renal function of the patient, she initially received fluconazole (0.4 g every day intravenously), amphotericin B (increasing 5 mg every 2 or 3 days from 10 mg per day, maintaining 35 mg per day, accumulative dosage 660 mg), and 5-fluorocytosine (1 g every 6 h, orally) for 4 weeks. During maintenance therapy with fluconazole (0.4 g every day intravenously), the patient developed fever and worsening skin lesion in the right leg. Liposomal amphotericin B (AmBisome, 50 mg every day) in combination with fluconazole (0.4 g every day intravenously) was initiated and continued for 11 weeks, followed by fluconazole (0.3 g every day orally) lifelong. After 3 years of follow-up, the leg lesions improved with post-inflammatory hyperpigmentation and scarring, without evidence of recurrence.

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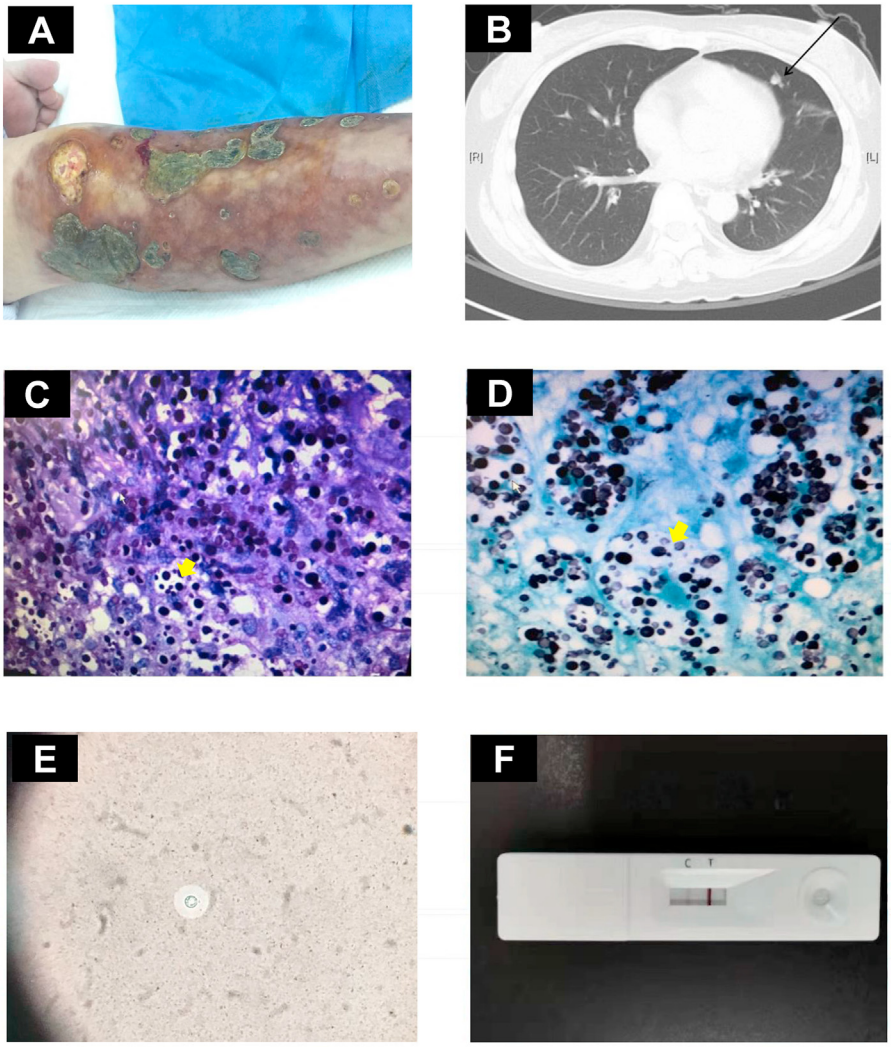

Figure 1. Disseminated cryptococcosis in a 33-year-old female patient underwent renal transplantation. (A) Erythematous plaques with oozing ulcers on the right leg. (B) Computed tomography revealed a nodular lesion (arrow) over the upper lobe of the left lung. Biopsy of the lesions demonstrated many yeast cells by (C) Periodic acid—Schiff and (D) Grocott's methenamine silver stains. (E) India ink staining of the patient's CSF revealed *cryptococcus*. (F) Positive result of the patient's CSF using Dynamiker CrAg LFA. C: control line; T: test line.

In this case, early diagnosis of cryptococcosis could be made using the positive CrAg LFA in the serum and CSF, which is now the preferred POC test due to its higher sensitivity, higher specificity, rapidity (turn-around time 15 min) and lower cost than India ink stains, culture, Chest examination and CrAg Latex agglutination (LA) methods.[3] The pooled sensitivity and specificity of CrAg LFA in 12 studies were 97.6% and 98.1% in serum samples and 98.9% and 98.9% in CSF samples.[5] The CrAg was found positive earlier than the clinical symptoms by 22 d (median value). About one third of asymptomatic CrAg-positive patients have concurrent cryptococcal meningitis.[4] A meta-analysis published in 2019 reported that, when no pre-emptive FCZ was taken in CrAg-positives patients, the incidence of mortality was 39.7%, apparently higher than 13.9% in CrAg negative patients.[5]

In a study conducted by Kwizera et al., compared to the IMMY CrAg LFA as the reference standard, the sensitivity of Dynamiker CrAg LFA was 98% in serum, 100% in plasma, and 100% in CSF from symptomatic patients, and 96% in serum from asymptomatic patients. They concluded that Dynamiker CrAg LFA had excellent sensitivity in comparison to the IMMY CrAg LFA.[3] Similarly, a recent study reported the Dynamiker CrAg LFA, used to diagnose cryptococcosis, also plays an important role in monitoring the disease.[6]

In conclusion, we reported a renal transplant recipient who had disseminated cryptococcosis involving central nervous system and skin, and may also including lung, demonstrating that CrAg LFA in the blood and CSF could be a primary microbiological tool for the early diagnosis of cryptococcosis.

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