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Abstract

Use of the PLEX-ID system can lead to a rapid molecular diagnosis in microbiology. To illustrate the clinical implications of this new diagnostic tool, we present the case of a 46-year-old patient admitted with severe respiratory failure and septic shock. Cryptococcal pneumonia was diagnosed by Fungi-Fluor™ staining of the bronchoalveolar lavage (BAL) and the patient tested positive for HIV. Unfortunately, he died 12h after admission despite intensive care support and treatment with broad-spectrum antibiotics, amphotericin B, and flucytosine. Retrospective use of the PLEX-ID on the BAL, bronchial aspirate, and blood yielded Cryptococcus neoformans in all fluids tested. Rapid molecular diagnosis with PLEX-ID, especially when performed on the blood of septic patients, may reduce the time to adequate treatment and limit the number of diagnostic procedures needed.

Reference


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Case Report

Fulminant atypical Cryptococcus neoformans pneumonia confirmed by PLEX-ID

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SUMMARY

Use of the PLEX-ID system can lead to a rapid molecular diagnosis in microbiology. To illustrate the clinical implications of this new diagnostic tool, we present the case of a 46-year-old patient admitted with severe respiratory failure and septic shock. Cryptococcal pneumonia was diagnosed by Fungi-FluorTM staining of the bronchoalveolar lavage (BAL) and the patient tested positive for HIV. Unfortunately, he died 12 h after admission despite intensive care support and treatment with broad-spectrum antibiotics, amphotericin B, and flucytosine. Retrospective use of the PLEX-ID on the BAL, bronchial aspirate, and blood yielded Cryptococcus neoformans in all fluids tested. Rapid molecular diagnosis with PLEX-ID, especially when performed on the blood of septic patients, may improve the time to adequate treatment and limit the number of diagnostic procedures needed.

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1. Introduction

The PLEX-ID system is a novel technology using multiplexed and broad-range PCR amplifications, coupled with electrospray ionization-mass spectrometry (ESI-MS) and computer triangulation to analyze the amplification products. It allows the identification of various pathogens within 4–6 h. This diagnostic tool should contribute to the earlier identification of pathogens, without the need to wait for culture. This may have a major impact on patient management and outcome, especially in immunocompromised patients, for whom empirical treatment cannot cover all possibilities.

2. Case report

A 46-year-old Mediterranean Caucasian man was seen in the emergency unit of our hospital with headache and dizziness for 15 days, without fever, impaired vision, or diplopia. His history was notable for a 10-kg weight loss in the preceding 2 months, without night sweats. The patient reported no prior medical visits and denied illicit drug use or high-risk sexual behavior. His blood pressure (BP) was 134/97 mmHg, heart rate (HR) 116 beats/min, temperature 37.6 °C, respiratory rate 14/min, and oxygen saturation 98% on ambient air; weight was 78 kg. Examination revealed no oral thrush, no lymphadenopathy, normal cardio-pulmonary auscultation, a supple neck, and normal neurological findings. The white blood cell count was 7.2 × 10^9/L, hemoglobin 128 g/l, and platelet count 120 × 10^9/L. Creatinine was 69 μmol/l and C-reactive protein (CRP) was 49 mg/dl. A cerebral computed tomography (CT) scan showed thickening of the mucosa of the left sphenoid sinus consistent with sinusitis. The patient was discharged with a prescription for oral amoxicillin–clavulanic acid, 625 mg three times daily, and consultation with his primary care physician to investigate the weight loss.

Five days later the patient developed severe dyspnea requiring ambulance transport to our emergency unit. Upon arrival his oxygen saturation was 72% on ambient air, BP was 125/61 mmHg, HR was 125 beats/min, and temperature was 37.8 °C. His respiratory rate was 35/min. Laboratory results showed a white blood cell count of 17.1 × 10^9/L, hemoglobin level of 156 g/l, and a
were of approximately Gram
quantitative with adenopathies
platelet was 112 mg/dl. Liver tests were normal and the lactate dehydro-
genase was 663 U/L.

Immediate interventions included endotracheal intubation, empiric broad-spectrum antibacterial therapy with imipenem-
cilastatin and clarithromycin, and pressure support with norepi-
nephrine and saline. CT of the brain, chest, and abdomen revealed
ground glass opacities obscuring the inferior lobes of both lungs.
There was also hepatosplenomegaly and retroperitoneal, mesen-
teric, mediastinal, and hilar lymphadenopathy (Figure 1). The
patient was admitted to the intensive care unit where bronch-
olevalveal lavage (BAL) showed $125 \times 10^9$ cells/ml comprising 88% macrophages and 10% polymorphonuclear cells.
Gram stain revealed no organisms. Fungi-Fluor\textsuperscript{TM} stain for
Pneumocystis jirovecii was negative, but revealed yeasts compatible with
Cryptococcus neoformans. PLEX-ID was also performed 5 days after
patient admission. This was performed with the BAL, bronchial aspirate, and blood, which were all positive for C.
neoformans. Respiratory virus PCR was positive for parainfluenza 2.
PCR for Chlamydia pneumoniae and Mycoplasma pneumoniae
were negative, as were serum and urinary antigens for Streptococ-
cus pneumoniae and Legionella spp.

A positive rapid HIV test was confirmed by immunoblot;
quantitative testing showed HIV-1 viremia at $7.3 \times 10^4$ copies/ml.
In view of the HIV-positive status with C. neoformans pneumonia,
our patient was categorized as HIV stage IV.

Immediately after the positive BAL for C. neoformans, about 6 h
after patient admission, amphotericin B and fluconosine therapy was added. Despite aggressive management, the patient developed
acute respiratory distress syndrome (ARDS) requiring increasing
inotropic support. This was followed by multiple organ dysfunction
with septic shock. He went into cardiorespiratory arrest approximately 12 h after admission and was successfully resuscit-
tated, but went into arrest again and died approximately 13 h after
admission. The BAL culture was positive for C. neoformans on day 2,
bronchial aspirate on day 4, and blood cultures on day 7.

On day 5, for the purpose of evaluation, the PLEX-ID was
performed on BAL, bronchial aspirate, and blood of this patient. All
were positive for C. neoformans.

3. Discussion

The PLEX-ID system was originally developed with the support of
the biodefense agencies in the USA. The idea was to combine
several broad-range PCR amplifications coupled with ESI-MS
detection of the amplicons and computed triangulation, to identify
any pathogen (bacterial, viral, fungal) rapidly from specimens.\textsuperscript{1}

Later, Abbott Molecular acquired this tool and developed it
towards clinical microbiology, where its use has been focused on
clinical samples.\textsuperscript{2} Because the test uses pattern recognition rather
than a categorical readout, it is likely that ESI-MS will eventually
allow the detection of multiple agents in the same assay of the
same sample. While the method has not yet been reduced to a
clinical assay, sample presentation and processing for other MS
applications has proven highly cost-effective compared to
conventional methods, saving both materials and labor costs as
well as improving turnaround times.\textsuperscript{3} We anticipate that this
modality will eventually take its place as a central element in
laboratory diagnostics for patients with unknown infections.
In this case, had such a test been applied to blood at the patient’s
initial presentation, it may have prevented his death.

PLEX-ID detected C. neoformans in the BAL, the bronchial
aspirate, and the blood culture bottles from this patient.
Interestingly, the PLEX-ID also revealed the presence of C.
neoformans directly from 1 ml of native blood in ethylenediamine-
netraacetic acid (EDTA). We are unable to assess whether the fungus would have been detected 5 days earlier when the patient
first presented. At that time there was no indication for exhaustive
testing and we had no residual sample to test. We note that some
public health agencies now recommend universal rapid HIV testing
for patients in this age group, regardless of the stated risk factors.\textsuperscript{4}

Had this been standard procedure, the outcome for this patient
might have been different.

Cryptococcosis is an opportunistic fungal infection with a
ubiquitous distribution mainly affecting AIDS patients, although
other immunocompromised and some immunocompetent patients
have also been infected. In a large series of 171 patients in
Brazil, Rozenbaum and Gonçalves found disseminated disease in
the vast majority (92%) of patients, whereas localized pulmonary
involvement only occurred in 14 patients (8%).\textsuperscript{5}

In our case, the clinical picture of septic shock with ARDS in
an immunocompromised patient was atypical enough to be
solely attributed to a disseminated cryptococcal infection,
based on the direct examination of BAL and later confirmed by
blood cultures. This unusual case highlights the potential of
using a broad-scale molecular diagnostic method to obtain
a rapid microbiological diagnosis in complicated clinical situa-
tions, and reinforces the need to have a higher index of suspicion for HIV and its complications in patients with an
unknown HIV status.

Conflict of interest: All authors report no conflicts of interest.

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