False Negative Latex Antigen Testing in a Cirrhotic Patient with cryptococcosis: *a case report*

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BACKGROUND

- *Cryptococcus neoformans* is an ubiquitous fungal pathogen that predominantly affects immunocompromised patients
- Liver cirrhosis is a risk factor for disseminated cryptococcal disease in HIV- uninfected patients
- Literature on the presentation and optimal management of cryptococcal disease in HIV-uninfected, cirrhotic patients is limited

CASE REPORT

A 56 year old male with alcoholic cirrhosis presented with progressively worsening shortness of breath and subjective fevers. He also had been having mild headaches with no focal neurologic complaints.

His physical exam revealed decreased breath sounds in the right lower lobe. He did not have acites or signs of decompensated cirrhosis. His neurologic exam was normal.

The initial evaluation revealed a pleural effusion in the right lower lobe (*Fig 1)* which was drained. Four days later, the transudative fluid from the Bactec bottles grew *C. neoformans (Fig 2),* which was confirmed by Vitek automated testing. Fluconazole was started.

Serum HIV ELISA and cryptococcal latex antigen testing (LAT; Meridian Diagnostics, Inc., Cincinnati, OH) with prozone were negative *(Table 1),* as were blood cultures.. LAT of the lung isolate was positive. Brain imaging was normal.

Lumbar puncture was performed, with an opening pressure of 23. CSF studies showed: WBC=135 (94% lymphocytes), RBC=80, Glucose=51, and Protein=33. CSF cryptococcal LAT and PCR were negative, as were all cultures and other evaluation for infectious etiologies. Fluconazole was discontinued; ambisome and flucytosine were initiated.

The patient experienced acute kidney injury after two weeks of treatment requiring renal replacement therapy and intubation for pulmonary edema. His CSF pleocytosis improved though his opening pressures on repeated lumbar punctures were as high as 66. LAT continued to be negative.

After 3 weeks, CSF parameters normalized, and induction therapy was stopped. Diflucan consolidation was started along with weekly lumbar punctures.

Fig 1. CT scan of the chest demonstrating right lower lobe effusion

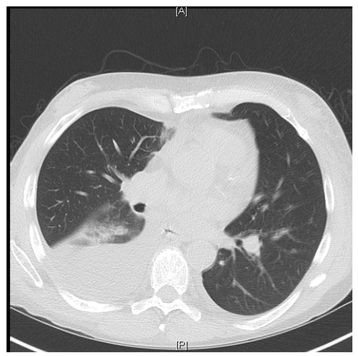

Fig 2. Gram stain of thoracentesis fluid with *C. neoformans*

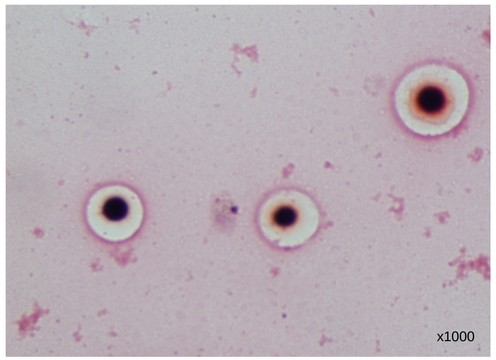

Table 1. Reported etiologies for false negative latex antigen testing and efforts to address them

Reason	Evaluation
Limitations of Meridian LAT kit	Sensitivity of 97-100% for serum and CSF; positive control done
Interference of other proteins with agglutination	Treatment of both serum and CSF samples with pronase
High burden of antigen	Both serum and CSF samples run with prozone
Variant organism (i.e., low level antigen producer, acapsular, or fastidious)	*In vitro,* capsule seen on Gram stain and antigen detected in pleural fluid
Low antigen level (i.e., pre-treatment or early in disease course)	Serial testing was done as disease progressed

DISCUSSION

Cryptococcal disease in HIV-uninfected cirrhotic patients most often presents as peritonitis or meningitis
- 20% of cirrhotic patients with cryptococcal disease will have evidence of dissemination
- In patients with pulmonary infection, cirrhosis is a risk factor for dissemination

Cryptococcal LAT is positive in >90% of patients with cryptococcosis
- Negative LAT is more common in HIV-uninfected patients or localized disease
- False negative LAT can be seen if early in disease, high antigen burden, or variant organisms present *(Table 1)*
- Host response may decrease capsule and/or antigen formation *in vivo* resulting in negative LAT
- Other reports have shown evidence of variant, antigen-negative organisms that become wild-type *in vitro*

Prognosis of cryptococcal disease in cirrhotic patients has been reported to be as high as 82%-100%, partly due to delay in diagnosis and treatment. In one series:
- The median time to detection of cryptococcus in peritoneal fluid was 6 days
- 38% of patients who died did not receive any antifungal therapy

Management is similar for HIV-infected and HIV-uninfected patients and includes combination induction therapy with ambisome and flucytosine. In those with meningitis, mortality is attributed to sequelae of increased intracranial pressure

CONCLUSIONS

- Liver cirrhosis is a significant risk factor for cryptococcal disease, particularly disseminated infection
- High clinical suspicion is needed, as diagnosis can be confounded by negative LAT
- Host factors leading to reduced capsule and/or antigen production *in vivo* may result in false negative LAT
- Early diagnosis and initiation of anti-fungal therapy along with management of elevated intracranial pressures are crucial to survival

REFERENCES

Baddley JW, Perfect JR, Oster RA, Larsen RA, Pankey GA, Henderson H, Haas DW, Kauffman CA, Patel R, Zaas AK, Pappas PG. Pulmonary cryptococcosis in patients without HIV infection: factors associated with disseminated disease. *Eur J Clin Microbiol Infect Dis*. 2008; 27: 937-943.

Chuang YM, Ho, YC, Chang HT, Yu CJ, Yang PC, Hsueh PR. Disseminated cryptococcosis in HIV-uninfected patients. *Eur J Clin Microbiol Infect Dis.* 2008; 27: 307-310.

Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, Harrison TS, Larsen RA, Lortholary O, Nguyen MH, Pappas PG, Powderly WG, Singh N, Sobel JD, Sorrell TC. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. *CID*. 2010; 50: 291-322.

Singh N, Husain S, de Vera M, Gayowski T, Cacciarelli TV. *Cryptococcus neoformans* infection in patients with cirrhosis, including liver transplant candidates. *Medicine.* 2004; 83: 188-192.

To KKW, Cheng VCC, Tang BSF, Fan Y, Yuen K. False-negative cerebrospinal fluid cryptococcal antigen test due to small-colony variants of *Cryptococcus neoformans* meningitis in a patient with cystopleural shunt. *Scand J Infect Dis*. 2006; 38: 110-114.

Yehia BR, Eberlein M, Sisson SD, Hager DN. Disseminated cryptococcosis with meningitis, peritonitis, and cryptococcemia in a HIV-negative patient with cirrhosis: a case report. *Cases Journal.* 2009; 2: 170-174.