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Original Article

Cryptococcus neoformans and PLWH: the role of serum cryptococcal antigen screening

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Abstract

Introduction: Serum cryptococcal antigen (CrAg) screening is crucial for early diagnosis of cryptococcal meningitis. This study presents the results of CrAg screening among people living with HIV (PLWH) followed in our clinic over the past six years.

Methodology: Patients with a CD4+ T cell count below 200 cells/µL who were tested for CrAg were included in the study. Data regarding age, gender, comorbidities, CD4+ T cell count, HIV RNA level, blood culture results, and cerebrospinal fluid (CSF) findings—including CrAg, microscopy, culture, and PCR—were retrospectively collected. Descriptive statistical methods were used for the analysis.

Results: Serum CrAg testing was performed on 99 patients, nine of whom tested positive. Among the patients with positive antigenemia, four were diagnosed with cryptococcal meningitis. In two cases, serum CrAg positivity was interpreted as false-positive due to the absence of clinical or laboratory findings consistent with cryptococcal infection. One patient died shortly after the CrAg test and could not be further evaluated. Two patients were lost to follow-up; however, one of them presented with symptoms two months later and was diagnosed with cryptococcal meningitis. Additionally, there was one patient with confirmed cryptococcal meningitis despite an initial negative serum CrAg result.

Conclusions: CrAg positivity may be detected during the asymptomatic phase of cryptococcal infection. Although current guidelines recommend serum CrAg screening for individuals with CD4+ T cell counts below 100 cells/µL, the detection of positive results in those with CD4+ T cell counts above this threshold should also be carefully evaluated, considering the possibility of false-positive or false-negative results.

Key words: Cryptococcal meningitis; antigen; CrAg; screening; HIV.

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Introduction

Cryptococcal infections are invasive fungal infections commonly observed in immunosuppressed patients. While *Cryptococcus neoformans* is the most frequently identified causative agent, *Cryptococcus gattii* can also be encountered in endemic regions [1]. Although the incidence of cryptococcal infections has declined with the widespread use of antiretroviral therapy (ART) among individuals living with HIV, it remains a significant cause of high-mortality opportunistic infections. Globally, it is estimated that there are 152,000 (111,000-185,000) cases of cryptococcal meningitis and 112,000 (79,000-134,000) cryptococcus-related deaths annually. Cryptococcosis accounts for 19% (13-24) of AIDS-related deaths worldwide [2]. It is known to be more prevalent in patients with a CD4+ T cell count < 100 cells/ µL. The disease often presents in the form of meningoencephalitis. Serum cryptococcal antigen (CrAg) is essential for diagnosis both during symptomatic and asymptomatic periods. While guidelines recommend screening patients with CD4+ T cell counts < 100 cells/µL, testing in patients with CD4+ T cell counts < 200 cells/µL has also been suggested in certain regions [3]. In this study, we aimed to determine the prevalence of serum CrAg positivity among patients followed in our clinic, evaluate its role in early diagnosis, examine its association with clinical findings, and compare it with simultaneous results from other diagnostic methods.

Methodology

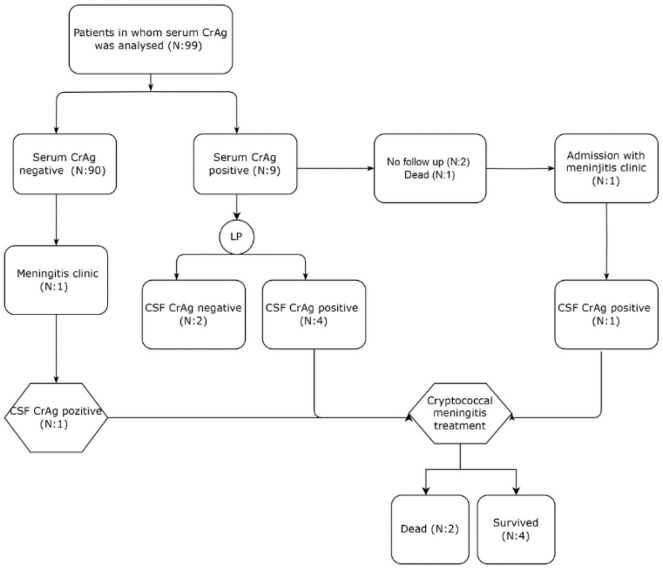
Patients aged 18 and older with a CD4+ T cell count < 200 cells/ µL, who were followed as inpatients or outpatients between January 1, 2017, and January 1, 2024, were included in the study. HIV-negative

individuals and patients with a history of cryptococcal meningitis were excluded from the study. Serum CrAg results of eligible patients were retrospectively evaluated. Clinical findings, cerebrospinal fluid (CSF) findings (CrAg results, cell counts, biochemical analyses, cultures, multiplex PCR results, blood culture results), and the methods used for CrAg detection were retrospectively analyzed for patients with positive serum CrAg detected through the hospital system.

Diagnostic categories were defined as follows: A "confirmed case" referred to patients exhibiting clinical signs consistent with cryptococcal meningitis, supported by positive CSF findings, such as culture growth of *Cryptococcus neoformans*, positive CSF CrAg, or positive multiplex PCR results. A "false positive" was considered when the serum CrAg test yielded a positive result, but subsequent evaluations, including clinical assessment and laboratory investigations (e.g, CSF analysis and blood cultures), did not support the presence of cryptococcal infection. An "indeterminate outcome" was assigned to instances where the serum CrAg test was positive, but the patient's clinical course could not be fully evaluated due to loss to follow-up or insufficient data, preventing a definitive classification. CSF samples were incubated for five days by inoculating onto routine bacteriology media. Blood cultures were performed using the BD Bactec FX Automated System (BD Diagnostics, Sparks, MD) between 2017-2020, and the BACT/ALERT 3D (Biomerieux Diagnostics) automated system between 2020-2023. The FilmArray Meningitis/Encephalitis (ME) Panel (Biofire-M/E Paneli (bioMérieux)) was used for syndromic meningitis multiplex PCR testing. The Dynamiker Cryptococcal Antigen Lateral Flow Assay (Dynemiker Diagnostics) was used for cryptococcal antigen testing.

The approval certificate numbered 4208 was obtained from the University of Health Sciences, Şişli Hamidiye Etfal Training and Research Hospital, Health Practice and Research Center Clinical Research Ethics Committee on 19.12.2023 for the study titled "Cryptococcal Antigen Screening in People Living with HIV (PLWH).

Figure 1. Patients' selection.



Results

A total of 99 PLWH who met the inclusion criteria were included in the study. Sixteen patients (16%) were female, and eighty-three (84%) were male. The age range of the patients was 23-94 years, with a mean age of 41 years. The median CD4+ T cell count was 40 cells/µL (IQR [17,3-82,7]). The median HIV RNA level was 692,397 copies/mL (IQR [283,000-1.631.938]). Serum cryptococcal antigen was positive in nine patients. Among these patients, the median CD4+ T cell count was 42 cells/µL, and the median HIV RNA level was 687,000 copies/mL.

Cryptococcal meningitis was clinically present in four patients, all of whom exhibited *C. neoformans* growth in both blood and CSF cultures, along with positive CSF cryptococcal antigen results. When CSF findings in these patients were examined, leukocyte counts ranged from 10-280/mm3, CSF glucose levels ranged from 19-48 mg/dl, and CSF protein levels ranged from 19-246 mg/L. One of these patients was lost to follow-up on the 19th day of hospitalization. Another patient, who was being followed for Pneumocystis pneumonia (PCP) and did not have meningitis symptoms, was found to have positive serum cryptococcal antigen results after hospitalization but before discharge. Further evaluation could not be performed as the patient did not return for follow-up after discharge. Approximately two months later, the patient presented to the outpatient clinic with headaches and was admitted. *Cryptococcus neoformans* was isolated from the patient's blood culture. The CSF analysis revealed 4 leukocytes/mm³, a CSF glucose level of 37 mg/dL, and a CSF protein level of 246 mg/L. The CSF cryptococcal antigen was also positive, and the meningitis multiplex PCR test detected *C. neoformans.* This patient was the only case who initially had asymptomatic serum CrAg positivity and later developed meningitis symptoms (Table 1, Patient 4).

In two patients who exhibited serum antigen positivity but lacked meningitis symptoms, with

negative blood cultures and CSF findings not suggestive of meningitis, the serum CrAg positivity was considered false positive (Table 1, Patients 7–8).

One patient was asymptomatic at the time of serum CrAg test positivity, but further investigation could not be performed as the patient was lost to follow-up. (Table 1/ Patient number 9) Another patient, who was being followed for hemophagocytic syndrome (HFS), died before the serum CrAg test result could be obtained (Table 1, Patient 10).

One additional patient diagnosed with cryptococcal meningitis had a negative serum CrAg test result. However, based on clinical findings, the CSF sample showed 214 leukocytes/mm3, CSF glucose level of 22 mg/dl, and CSF protein level of 46 mg/L. CSF CrAg was positive*, C. neoformans* was isolated from the CSF culture, and the meningitis multiplex PCR test was positive for *C. neoformans*. This patient, who also had concomitant *Salmonella typhi* bacteremia, died on the 13th day of follow-up (Table 1, Patient 6).

The flowchart of the patients in the study is presented in Figure 1.

When CD4+ T cell counts among patients with positive CrAg tests were evaluated, seven patients had CD4+ T cell counts < 100 cells/μL, and two patients had counts > 100 cells/μL. While one of the cases with CD4+ T cell counts > 100 cells/ μL was considered a false positive, the other could not be evaluated as the patient was lost to follow-up despite positivity detection.

Discussion

In primary infections with *Cryptococcus spp*, yeast cells or basidiospores acquired through inhalation are usually controlled by immune mechanisms, leading to a latent infection. However, in cases of immunosuppression, the reactivation of the infection can lead to cryptococcosis. The clinical presentation often manifests as meningoencephalitis. Before the onset of meningitis symptoms, asymptomatic cryptococcal antigen (CrAg) positivity can be detected in serum. Studies have shown that meningitis symptoms typically develop approximately 22 days after the detection of cryptococcal antigenemia [4]. The clinical presentation often manifests as meningoencephalitis. In our patient, who initially had asymptomatic serum CrAg positivity but later presented with symptoms such as fatigue, chills, intermittent cough, headache, and toothache, there was approximately a 60-day gap between the detection of serum CrAg positivity and the diagnosis of cryptococcal meningitis. This delay might be attributed to the nonspecific natüre of early

Table 1. Patients with Serum / CSF CrAg Positivity.

Patient no	Age	CD4 Count (cells/mL)	*Serum CrAG*	CSF Findings	CSF Microscopy	CSF CrAG	CSF Culture	Blood Culture	CSF PCR	Diagnosis / Follow-up
1	44	6	Positive	10 Leukocytes/mm^3; Glucose: 9 mg/dl; Protein: 87 mg/L	Encapsulated yeast cells observed	Positive	*C. neoformans*	*C. neoformans*	Positive for *C. neoformans*	Cryptococcal meningitis
2	27	42	Positive	150 Leukocytes /mm^3; Glucose: 29 mg/dl; Protein: 87 mg/L	Encapsulated yeast cells observed	Positive	*C. neoformans*	*C. neoformans*	x	Cryptococcal meningitis/ Dead
3	28	56	Positive	280 Leukocytes/mm^3; Glucose: 20 mg/dl; Protein: 246 mg/L	Encapsulated yeast cells observed	Positive	*C. neoformans*	*C. neoformans*	Positive for *C. neoformans*	Cryptococcal meningitis
4	39	36	Positive	4 Leukocytes /mm^3; Glucose: 37 mg/dl; Protein: 246 mg/L	No microorganism observed	Positive	*C. neoformans*	*C. neoformans*	Positive for *C. neoformans*	Cryptococcal meningitis
5	24	5	Positive	10 Leukocytes /mm^3; Glucose: 48 mg/dl; Protein: 22 mg/L	x	x	*C. neoformans*	*C. neoformans*	Positive for *C. neoformans*	Cryptococcal meningitis
6	42	7	Negative	214 Leukocytes /mm^3; Glucose: 22 mg/dl; Protein: 46 mg/L	x	Positive	*C. neoformans*	-	Positive for *C. neoformans*	Cryptococcal meningitis/Dead
7	53	105	Positive	3 Leukocytes /mm^3; Glucose: 50 mg/dl; Protein: 34 mg/L	No microorganism observed	Negative	Negative	Negative	Negative	False positive
8	53	93	Positive	5 Leukocytes/mm^3; Glucose: 53 mg/dl; Protein: 52 mg/L	No microorganism observed	Negative	Negative	Negative	Negative	False positive
9	36	117	Positive	-	-	-	-	-	-	Unknown
10	25	25	Positive	-	-	-	-	-	-	Dead

PCR: polymerase chain reaction; CSF:Cerebrospinal Fluid; CrAG: Cryptococcal Antigen.

symptoms of, different clinical interpretations due to coexisting diseases, and the patient's delayed presentation to the hospital.

The prevalence of CrAg positivity varies by geographic regions and CD4+ T cell counts. Studies indicate that the positivity rate is between 6% and 13% in individuals with CD4+ T cell counts below 100 cells/μL, and between 3% and 11% in those with counts below 200 cells/μL [5-7]. In our study, serum CrAg positivity was detected in nine patients: seven with CD4+ T cell counts below 100 cells/μL and two with counts above 100 cells/μL.

For CrAg diagnosis, methods such as lateral flow assay (LFA), latex agglutination (LA), and enzyme immunoassay (EIA) are available. The LA test is manual, subjective, and time-consuming, with serum sensitivity ranging from 97.0% to 97.8% and specificity from 85.9% to 100% [8]. The EIA is a microplate-based method with sensitivity ranging from 55.6% to 100% and specificity from 99% to 100% [9]. The LFA test is the most widely used method globally due to its ease of use, low cost, high sensitivity (97.0%-97.8%), and high specificity (85.9%-100%), and is recommended by the World Health Organization for the diagnosis of cryptococcosis [8-10]. Although the rate of false negatives is very low, some reports have noted such occurrences in some cases, have been reported [11].

Among those with cryptococcal meningitis, one had a negative serum CrAg test via LFA but positive CSF CrAg and positive *Cryptococcus neoformans* cultures from CSF. This case is significant as it represents a rare instance of false-negative serum CrAg results in cryptococcal meningitis. False-negative CrAg results can occur due to low fungal burden, prozone reactions from high antigen titers, the presence of immune complexes that inhibit antigen release, improper sample handling, or infections caused by hypoglucan or acapsular *Cryptococcus* spp. infections due to acapsular *Cryptococcus* or poorly encapsulated strains are typically diagnosed only through tissue biopsy or culture [12,13].

Although false-positive CrAg results are rare, they have been reported in the literature. In a series of seven cases with false-positive serum CrAg results, four cases used the LA test and three used the LFA test. One LA test case involved a patient with systemic lupus erythematosus (SLE), where nonspecific interference from circulating autoantibodies was suggested. Other cases involved infections with *Trichosporon asahii, Stomatococcus*, and *Capnocytophaga*, with low titers seen in false-positive LA tests. Insufficient dilution was considered the cause of false positivity in the three LFA test cases [14]. In our study, serum CrAg positivity was considered false-positive in two asymptomatic cases, neither of whom had autoimmune disease or fungal infection. One patient had cerebral toxoplasmosis, and the other had tuberculosis lymphadenitis. These conditions have not been associated with false positivity in the literature, suggesting that the false positives may be related to the testing method.

Studies have shown a significant association between antigenemia and mortality. Six months after HIV diagnosis, the overall mortality rate among CrAg-positive individuals was 11.8%, compared to 3.7% among CrAg-negative individuals. Additionally, delays in CrAg testing have been associated with increased mortality and hospitalizations [4]. In our study, no significant difference in mortality rates between CrAg-positive and CrAg-negative patients was observed after six months. The relationship between CrAg testing timing and mortality could not be evaluated due to the small sample size.

A study evaluating the cost-effectiveness of serum CrAg testing in asymptomatic PLWH found that both CrAg-LA and CrAg-LFA were cost-effective [15]. Another study demonstrated that using CrAg-LFA in symptomatic PLWH was more cost-effective than using CrAg-LA [16].

One notable challenge with the LFA method in our center is that the test is performed off-site. Previously, the average turnaround time for test results was approximately 20 days; currently, results are obtained within 24 hours. Delays in test results can hinder further investigation and preemptive treatment, especially in asymptomatic patients. One of our patients had CrAg positivity detected after discharge, preventing further investigation. Another patient died before the serum CrAg test results were available, which were later found to be positive. In such rapidly progressing cases, the time required to obtain test results can be longer than the patient's expected lifespan, highlighting the value of quick access to test results.

Studies have shown an association between CSF protein levels and prognosis in cryptococcal meningitis. One study reported that CSF protein levels ≥ 100 mg/dL were significantly associated with increased seizure frequency, lower Glasgow Coma Scale scores, and poor prognosis [17]. Among our cryptococcal meningitis patients, two had CSF protein levels ≥ 100 mg/dL; however, no mortality was observed in these patients. Due to the small sample size, the relationship between CSF protein levels and clinical outcomes could not be evaluated.

Culture remains the gold standard for diagnosing

cryptococcosis. In PLWH with cryptococcal meningitis, blood cultures are positive in 50% of cases, while CSF cultures are positive in 80%. *Cryptococcus* colonies are typically detectable within 3-7 days on Sabouraud dextrose agar. Gram staining shows weakly stained Gram-positive yeasts, and India ink staining reveals encapsulated yeast cells in 60-80% of cases [18]. Among our six patients with cryptococcal meningitis, five (83.3%) had positive blood cultures, and all six (100%) had positive CSF cultures for *C. neoformans*. Encapsulated yeast cells were observed in CSF with India ink staining in four patients.

Polymerase chain reaction (PCR) is another method increasingly used in clinical practice. While some studies report near 100% sensitivity and specificity, sensitivity may decrease to 50% in cases with low fungal burden, leading to false-negative results [19]. Thus, combining PCR with serum and CSF CrAg tests is recommended. The high cost of PCR limits its widespread use. Among our six patients with cryptococcal meningitis, five had positive CSF multiplex PCR results for *C. neoformans.*

One limitation of our study was the small sample size. Although our center follows a large number of PLWH, the number of patients with CD4+ T cell counts below 200 cells/μL, and consequently the number diagnosed with cryptococcal meningitis, was low due to the increased use of ART and early diagnosis. The literature also reports a decreased incidence of cryptococcal infections in PLWH following effective ART [2].

A case series from Turkey published between 1953 and 2003 reported 41 cases of cryptococcosis. Central nervous system involvement was observed in 30 cases, pulmonary involvement in one case, colonic involvement in one case, and six disseminated cases. Seven of these patients were PLWH [20]. Another publication reported the prevalence of cryptococcal meningitis in Turkey as 0.13 per 100,000 individuals [21]. More comprehensive studies are needed to determine the prevalence of cryptococcal infection in PLWH in Turkey.

Conclusions

Cryptococcal meningitis remains an important opportunistic infection among individuals living with HIV, particularly those with low CD4+ T cell counts. While various diagnostic tests are available, the CrAg test is distinguished by its ability to provide opportunities for preemptive treatment. Screening strategies should be planned regionally based on the prevalence of cryptococcal infection. Efforts should also be made to ensure rapid-result testing. The integration of CrAg screening into national HIV care protocols may facilitate timely diagnosis and management of cryptococcal infections, especially in resource-limited settings where HIV burden is high.

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Conflict of interest

No conflict of interest is declared.

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