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Recurrence of Symptoms Following Cryptococcal Meningitis: Characterizing a Diagnostic Conundrum With Multiple Etiologies

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Background. Cryptococcal meningitis is a common cause of AIDS-related mortality. Although symptom recurrence after initial treatment is common, the etiology is often difficult to decipher. We sought to summarize characteristics, etiologies, and outcomes among persons with second-episode symptomatic recurrence.

Methods. We prospectively enrolled Ugandans with cryptococcal meningitis and obtained patient characteristics, antiretroviral therapy (ART) and cryptococcosis histories, clinical outcomes, and cerebrospinal fluid (CSF) analysis results. We independently adjudicated cases of second-episode meningitis to categorize patients as (1) microbiological relapse, (2) paradoxical immune reconstitution inflammatory syndrome (IRIS), (3) persistent elevated intracranial pressure (ICP) only, or (4) persistent symptoms only, along with controls of primary cryptococcal meningitis. We compared groups with chi-square or Kruskal-Wallis tests as appropriate.

Results. 724 participants were included (n = 607 primary episode, 81 relapse, 28 paradoxical IRIS, 2 persistently elevated ICP, 6 persistent symptoms). Participants with culture-positive relapse had lower CD4 (25 cells/μL; IQR: 9–76) and lower CSF white blood cell (WBC; 4 cells/μL; IQR: 4–85) counts than paradoxical IRIS (CD4: 78 cells/μL; IQR: 47–142; WBC: 45 cells/μL; IQR: 8–128). Among those with CSF WBC <5 cells/μL, 86% (43/50) had relapse. Among those with CD4 counts <50 cells/μL, 91% (39/43) had relapse. Eighteen-week mortality (from current symptom onset) was 47% among first episodes of cryptococcal meningitis, 31% in culture-positive relapses, and 14% in paradoxical IRIS.

Conclusions. Poor immune reconstitution was noted more often in relapse than IRIS as evidenced by lower CSF WBC and blood CD4 counts. These easily obtained laboratory values should prompt initiation of antifungal treatment while awaiting culture results.

Clinical Trials Registration. NCT01802385.

Keywords. cryptococcosis; cryptococcal meningitis; immune reconstitution inflammatory syndrome; relapse; meningitis.

Cryptococcal meningitis remains the most common cause of meningitis in sub-Saharan Africa and is a major contributor to human immunodeficiency virus (HIV)–associated mortality, contributing to an estimated 19% of AIDS-related mortality globally [1]. As antiretroviral therapy (ART) coverage has improved, the proportion of cryptococcal meningitis cases occurring in persons receiving ART has increased [1, 2]. This dynamic has led to increasing case complexity often related to the recurrence of cryptococcal meningitis symptoms.

Second episode of cryptococcal meningitis refers to the recurrence of meningitis symptoms in those with a prior history of cryptococcal meningitis. Symptoms may recur for a variety of reasons. First, a true microbiologically proven, culture-positive relapse of cryptococcal meningitis may occur due to inadequate or incomplete treatment of the prior meningitis episode, including early cessation of maintenance therapy [3–5]. Paradoxical immune reconstitution inflammatory syndrome (IRIS) occurs in a patient with microbiological and clinical improvement when symptoms recur after immune reconstitution (in this case due to ART); clinically, the patient's presentation may be very similar to that of a microbiological relapse but the etiology is immunologic [3, 6]. Additionally, symptomatic recurrence may occur due to a persistence of elevated intracranial pressure (ICP) in the absence of paradoxical IRIS or

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microbiological culture-positive relapse; or there may be recurrent symptoms despite no evidence of IRIS, recurrence of infection, or elevated pressure [7]. Finally, significant symptom overlap with other infections or noninfectious cause such as medication side effects or a cerebrospinal fluid (CSF) leak from prior lumbar puncture (LP) may be attributed to recurrence of cryptococcal meningitis [3].

Limited literature exists to guide the clinician through this complicated clinical scenario where numerous potential causes of symptoms exist. Cryptococcal antigen (CrAg) does not rapidly (or predictably) decay in the CSF [3, 8]; thus, CrAg is not diagnostically useful in second episodes. When a patient presents with recurrence of symptoms following cryptococcal meningitis, the treating physician is often left to perform an LP and consider re-instituting aggressive (potentially toxic) antifungal therapy while waiting multiple days for CSF culture results. We sought to characterize these patients with symptomatic second episodes of cryptococcal meningitis by etiology and further compare them with patients with first-episode cryptococcal meningitis to gain insights into patients' characteristics that might distinguish one etiology from another, and to better understand outcomes.

METHODS

Patients presenting with suspected cryptococcal meningitis were prospectively enrolled at Kiruddu Hospital and Mulago National Referral Hospital in Kampala, Uganda, as well as Mbarara Regional Referral Hospital in Mbarara, Uganda. Study screening and enrollment were part of an existing clinical trial (Adjunctive sertraline in HIV-associated cryptococcal meningitis [ASTRO-CM], NCT01802385) [2, 9, 10]. Individuals with a prior history of cryptococcal meningitis were excluded from ASTRO-CM but were consented to receive open-label, compassionate use of sertraline; study procedures were otherwise identical. Approvals were obtained from the Uganda National Council for Science and Technology local study site institutional review boards and the University of Minnesota. Participants or their surrogates provided written informed consent. Participants enrolled from August 2013 until May 2017 were part of ASTRO-CM. From June 2017 until November 2020, participants were enrolled into a continuation cohort and received standard-of-care treatments. Participants with suspected relapse or IRIS were initially screened. Additional consecutive cases after May 2017 of primary cryptococcal meningitis were included as controls.

Data Collection

Study data collection included demographics, symptoms and physical examination findings, information about prior HIV diagnosis, prior and current ART, prior cryptococcal meningitis diagnosis, and antifungal treatment before the current presentation. We report CD4 counts, evidence of tuberculosis (TB) at enrollment, and mortality at 14 days, 30 days, and 18 weeks, when available. Results from CSF laboratory testing (protein, glucose, cell count, and differential), CSF CrAg (lateral flow assay; IMMY, Norman, OK, USA) [8, 11], CSF fungal culture (Sabouraud dextrose agar), CSF smear for acid-fast bacilli, CSF mycobacterial culture, CSF GeneXpert MTB/Rif or GeneXpert MTB Rif Ultra (Cepheid, Inc, Sunnyvale, CA, USA), and the CSF Biofire multiplex polymerase chain reaction (PCR) meningitis/encephalitis panel (Biomerieux, Salt Lake City, UT, USA) were collected. Where CSF white blood cell (WBC) counts were less than 5 cells/μL (the lower limit of the assay), 4 cells/μL was substituted when needed to calculate descriptive statistics. Results from metagenomic next-generation sequencing (mNGS) were available on some stored specimens [12].

Adjudication of the Etiology of the Current Presentation

Patients with a history of cryptococcal meningitis prior to enrollment were independently reviewed by 2 authors (C. P. S. and N. C. B.) to categorize the cause of their presentations. Any disagreements were resolved by consensus discussion. Cases known to be first presentations of cryptococcal meningitis were included. Additional participants were categorized as follows: (1) relapse of cryptococcal meningitis, defined as clear improvement in symptoms from prior episode of cryptococcal meningitis before presentation noted by the clinical team providing care and growth of *Cryptococcus* on CSF fungal culture; (2) paradoxical IRIS, defined as clear improvement in symptoms from the prior episode of cryptococcal meningitis before presentation, change in ART regimen, or improved ART adherence following prior episode and before current episode and negative CSF fungal culture [13]; (3) persistent elevation of opening pressure, defined as clear improvement in symptoms from prior episode of cryptococcal meningitis before presentation, no growth on current fungal culture, no elevations of CSF cell count or protein, persistently elevated CSF opening pressure above 250 mmH_2O on second presentation with improvement in symptoms with LP; or (4) isolated persistent symptoms, defined as improvement in symptoms from prior episode of cryptococcal meningitis before presentation, no growth on current fungal culture, no elevations of CSF cell count or protein, no elevated opening pressure, and recurrent symptoms at the second presentation (Figure 1). Lack of CSF inflammation (protein and WBC) was included in the last 2 group definitions to guard against inclusion of atypical IRIS that did not fit the typical definition [13] of IRIS or undiagnosed alternative infections. Each of the 4 definitions also specified that there was no evidence of concomitant central nervous system infection with another pathogen. All cases not meeting these definitions were excluded from analysis including those with coinfections, persistent cryptococcal infection (where

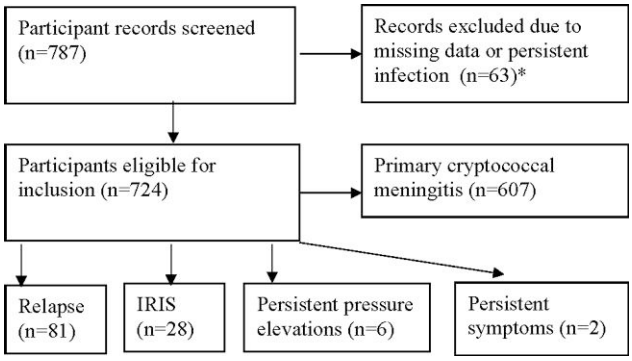

Figure 1. Summary of participant inclusion. *Seventeen excluded due to persistent infection, 46 due to missing data. Missing data in this context refers to incomplete data, such that an adjudication could not reasonably be determined; missing data that did not change the ability to adjudicate the cause of the syndrome were allowed.

symptoms had never improved and cultures remained positive), and cases where adjudication was impossible due to missing information.

Statistical Analysis

Groups were compared with chi-square and Kruskal-Wallis tests, as appropriate. There was no adjustment for multiple comparisons. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used. Due to small numbers, participants with persistently elevated opening pressures or persistent symptoms are described separately without statistical comparison.

RESULTS

A total of 787 participants were screened. Of those, 63 were excluded due to inability to adjudicate a cause because of missing information (n = 46), or because their presentation was determined to be due to a persistent infection (n = 17) (Figure 1). The remaining 724 were grouped as follows: 607 with primary infection, 81 with culture-positive relapse, 28 with paradoxical IRIS, 2 with persistently elevated ICP without IRIS or relapse, and 6 with persistent symptoms but no evidence of relapse, IRIS, or elevated opening pressure.

Table 1 describes baseline characteristics of those with primary cryptococcal meningitis, microbiologically proven relapse, and IRIS. Fever and cough were more common in primary cryptococcal meningitis than in relapse or IRIS. Time from HIV diagnosis to presentation was shorter in primary episodes (2.7 months; interquartile range [IQR]: 0.2–34.2 months) compared with relapse (22.6 months; IQR: 7.2–72.2 months) or IRIS (39.9 months; IQR: 7.8–51.5 months) ($P <$ .001 comparing all 3 groups, $P = .94$ comparing IRIS and relapse). Most patients with IRIS or relapse were receiving ART at presentation but less than half of those with primary cryptococcal meningitis were receiving ART. Second-line ART use was also more common among those with IRIS (6/18, 33%) or relapse (16/56, 29%) than first episodes (28/240, 12%) ($P < .001$). Median CD4 counts were higher in IRIS (78 cells/μL; IQR: 47–142) compared with relapse (25 cells/μL; IQR: 9–76) ($P < .01$). Of those presenting in second episodes with CD4 counts less than 50 cells/μL, 91% (39/43) had relapse. Both relapse and IRIS groups had higher mean CD4 counts than primary episodes.

Table 2 describes CSF parameters from those with primary cryptococcal disease, relapse, or IRIS. Intracranial pressures were higher in relapse (330 mmH_2O; IQR: 212–500) compared with primary episodes (270 mmH_2O; IQR: 180–390) ($P = .02$). Median CSF WBC was highest among those with IRIS (45 cells/μL; IQR: 8–128) compared with those with relapse (4 cells/μL; IQR: 4–85) or primary cryptococcal meningitis (<5 cells/μL; IQR: 4–40) ($P < .001$). Of those with a CSF WBC count less than 5 cells/μL, 86% (43/50) had relapse. Log_{10}-transformed values of CSF culture colony counts were higher in primary episodes (4.7 colony-forming units [CFU]/mL log_{10}; IQR: 3.1–5.5) compared with relapse (3.2 CFU/mL log_{10}; IQR: 2.3–4.8) ($P < .001$).

Metagenomic next-generation sequencing data were available for 21 of the 117 participants with relapse, IRIS, persistently elevated pressure, or persistent symptoms. Among those, 11 participants had been adjudicated to have relapse, of whom 10 had detectable *Cryptococcus neoformans* (the other participant had no pathogen detected, but *C. neoformans* was found on culture). No pathogen was identified in the other 10 participant samples, of whom 9 had been adjudicated as IRIS and 1 as having persistent symptoms in the absence of relapse, IRIS, or elevated ICP. Results were available for the multiplex PCR assay [14] from 20% (116/607) of participants with primary cryptococcal meningitis, 11% (9/81) of those with relapse, and 14% (4/28) with IRIS. No pathogens were identified in any IRIS cases. Among the 9 relapse cases, 4 had no pathogen identified and 5 had *Cryptococcus* species identified, of which one also had varicella zoster virus identified. Among primary episode cases, 20.7% (24/116) had no pathogen identified, 61.2% (71/116) identified *Cryptococcus* species and no other pathogen, 13.8% (16/116) identified *Cryptococcus* species and another pathogen, and 4.3% (5/116) identified only another pathogen. Other pathogens are shown in Table 3.

Table 4 and Figure 2 show mortality data starting from the current presentation. Fourteen-day mortality was higher among those with initial-episode cryptococcal meningitis (27.5%, 167/607; $P < .01$) than in relapse cases (12.3%, 10/81) or those with IRIS (14.3%, 4/28). Eighteen-week mortality was also highest among initial cryptococcal meningitis cases at 47.3% (287/607) followed by relapse cases at 30.9% (25/81) and those with IRIS at 14.3% (4/28) ($P = .09$ relapse vs IRIS). Interestingly, Figure 2 shows that at approximately 4 weeks, mortality from relapse passes that of IRIS (which stays stable),

Table 1. Baseline Characteristics Among Participants With Primary Cryptococcal Meningitis, Microbiologically Proven Relapse, and Paradoxical IRIS

	Initial Cryptococcal Meningitis (n = 607)		Culture-Positive Relapse (n = 81)		Paradoxical IRIS (n = 28)		
	Number With Data	Values	Number With Data	Values	Number With Data	Values	Overall *P* Values
Age, y	607	35 [30, 40]	81	35 [30, 42]	28	38 [32, 46]	.16
Male sex, n (%)	607	371 (61.1%)	81	52 (64.2%)	28	19 (67.9%)	.69
Headache presence, n (%)	605	594 (98.2%)	81	79 (97.5%)	28	28 (100.0%)	.70
Headache duration, d	592	14.0 [7.0, 28.0]	79	14.0 [7.0, 30.0]	27	14.0 [7.0, 14.0]	.10
Vomiting, n (%)	605	354 (58.5%)	80	43 (53.8%)	28	12 (42.9%)	.21
Seizures, n (%)	605	88 (14.5%)	80	12 (15.0%)	28	7 (25.0%)	.32
Fever, n (%)	605	319 (52.7%)	80	20 (25.0%)	28	6 (21.4%)	<.001
Cough, n (%)	605	135 (22.3%)	80	9 (11.3%)	28	2 (7.1%)	.01
Photophobia, n (%)	605	168 (27.8%)	80	19 (23.8%)	28	5 (17.9%)	.41
Time HIV positive,[a] mo	573	2.7 [0.2, 34.2]	67	22.6 [7.2, 72.2]	21	39.9 [7.8, 51.5]	<.001
On ART, n (%)	606	286 (47.2%)	81	73 (90.1%)	28	28 (100.0%)	<.001
Time on ART, mo	284	4.4 [0.8, 26.4]	72	7.3 [3.4, 18.5]	27	4.6 [2.1, 15.9]	.14
On second-line ART, n (%)	240	28 (11.7%)	56	16 (28.6%)	18	6 (33.3%)	<.001
CD4 cell count, cells/μL	578	15 [6, 47]	59	25 [9, 76]	12	78 [47, 142]	<.001
TB prevalent,[b] n (%)	607	45 (7.4%)	72	3 (4.2%)	22	1 (4.5%)	.54
Prior amphotericin, n (%)	607	73 (12.0%)	81	7 (8.6%)	28	0 (0.0%)	.11
Prior fluconazole, n (%)	574	31 (5.4%)	78	42 (53.8%)	28	8 (28.6%)	<.001
Prior fluconazole dose, n (%)	65		68		26		.51
200 mg		27 (41.5%)		31 (45.6%)		11 (42.3%)	
400–600 mg		9 (13.8%)		8 (11.8%)		7 (26.9%)	
800–900 mg		21 (32.3%)		24 (35.3%)		7 (26.9%)	
1200 mg		8 (12.3%)		5 (7.4%)		1 (3.8%)	
Current fluconazole, n (%)	574	37 (6.4%)	79	33 (41.8%)	28	20 (71.4%)	<.001
Months since prior CM	0	N/A	79	5.4 [3.1, 12.7]	28	6.5 [3.0, 14.3]	.82

Data are presented as median [interquartile range] or n (%). Prior fluconazole/amphotericin use refers to any indication prior to the current suspected meningitis episode.
Abbreviations: ART, antiretroviral therapy; CM, cryptococcal meningitis; HIV, human immunodeficiency virus; IRIS, immune reconstitution inflammatory syndrome; N/A, not applicable; TB, tuberculosis.

[a]Refers to time from HIV diagnosis to current presentation.

[b]Not TB meningitis.

Table 2. Cerebrospinal Fluid Characteristics Among Participants With Primary Cryptococcal Meningitis, Microbiologically Proven Relapse, and IRIS

	Initial Cryptococcal Meningitis (n = 607)		Culture-Positive Relapse (n = 81)		Paradoxical IRIS (n = 28)		
	Number With Data	Values	Number With Data	Values	Number With Data	Values	Overall *P* Values
CSF opening pressure, mmH_2O	533	270 [180, 390]	63	330 [212, 500]	24	265 [220, 360]	.07
CSF protein, mg/dL	518	47 [23, 100]	72	63 [30, 99]	26	103 [29, 160]	.02
CSF glucose, mg/dL	174	60 [38, 98]	20	39 [24, 64]	10	46 [24, 66]	.01
CSF WBC count, cells/μL	585	4 [4, 40]	80	4 [4, 85]	28	45 [8, 128]	<.001
CSF WBC count ≤5 cells/μL, n (%)	585	382 (65.3%)	80	43 (53.8%)	28	7 (25.0%)	<.001
CSF lymphocytes, %	217	100 [90, 100]	33	100 [100, 100]	18	100 [92, 100]	.30
CSF culture, log_{10} CFU/mL	603	4.7 [3.1, 5.5]	79	3.2 [2.3, 4.8]	25	0.0 [0.0, 0.0]	<.001*
CSF CrAg positive, n (%)	607	607 (100.0%)	81	81 (100.0%)	28	28 (100.0%)	

Data are presented as median [interquartile range] or n (%). *Compares initial cryptococcal meningitis and culture positive relapse.
Abbreviations: CFU, colony-forming units; CSF, cerebrospinal fluid; CrAg, cryptococcal antigen; IRIS, immune reconstitution inflammatory syndrome; WBC, white blood cell.

although as time goes on, the number of individuals with available data decreases.

Similar data were recorded among those with only either persistently high ICPs (n = 2) or persistent symptoms without high ICPs (n = 6) (Supplementary Tables 1 and 2). Given the small numbers involved, statistical comparisons were not completed. Median CD4 count was 18 cells/μL in those with persistently elevated ICPs compared with 92 cells/μL in those with persistent symptoms (n = 2/6). None in these groups had elevated CSF protein or WBC, had multiplex PCR available, or had died by 18 weeks.

Table 3. Results of Multiplex PCR Testing Among Participants With Primary Cryptococcal Meningitis, Microbiologically Proven Relapse, and IRIS

	Adjudicated Category		
	Initial Cryptococcal Meningitis	Culture Positive Relapse	Paradoxical IRIS
Number of participants	607	81	28
Number with Biofire data	116	9	4
No pathogen, n (%)	24 (20.7%)	4 (44.4%)	4 (100.0%)
Cryptococcus only, n (%)	71 (61.2%)	4 (44.4%)	0 (0.0%)
Cryptococcus and other pathogen, n (%)	16 (13.8%)	1 (11.1%)	0 (0.0%)
No *Cryptococcus*, has other pathogen, n (%)	5 (4.3%)	0 (0.0%)	0 (0.0%)
Other pathogens detected			
Human herpesvirus 6	6	0	0
Varicella zoster virus	3	1	0
Streptococcus pneumoniae	2	0	0
Haemophilus influenza	3	0	0
Cytomegalovirus	3	0	0
Herpes simplex virus 2	3	0	0
Herpes simplex virus 1	0	0	0

Data are presented as n (%) unless otherwise indicated. Results within 14 days of screening.
Abbreviations: IRIS, immune reconstitution inflammatory syndrome; PCR, polymerase chain reaction.

DISCUSSION

We present an analysis of recurrence of cryptococcal meningitis symptoms after seemingly successful initial treatment. We adjudicated these cases to 1 of 4 causes: (1) microbiologically proven relapse (by culture), (2) IRIS, (3) persistently elevated ICP causing symptom relapse without microbiological relapse or IRIS, or (4) recurrence of symptoms without microbiological relapse, IRIS, or elevated ICPs. We also compared patients with IRIS and relapse with patients with primary cryptococcal meningitis using numerous parameters.

Microbiological relapse is familiar to most clinicians who have treated a large volume of cryptococcal meningitis cases. Yet, while predictors of cryptococcal meningitis IRIS are well studied, publications on relapse, with the exception of case reports, are less common [3, 15, 16]. Further, the larger studies were primarily before widespread ART utilization in many countries [17, 18].

We found that time from HIV diagnosis to presentation was numerically (but not statistically) higher in IRIS compared with relapse. Shelburne and colleagues [18] found that, in their cohort, those with IRIS (n = 18) were more likely to have initiated ART (100%) and to have had robust virological and CD4 count responses (median increase: 93 cells/μL) compared with relapse (n = 12, 33%; 4 cells/μL). This differs from our findings in that we found high rates of ART usage in those with IRIS

Table 4. Outcomes Among Participants With Primary Cryptococcal Meningitis, Microbiologically Proven Relapse, and IRIS

Mortality	Initial Cryptococcal Meningitis (n = 607)	Culture-Positive Relapse (n = 81)	Paradoxical IRIS (n = 28)	*P*
Mortality by day 14	167 (27.5%)	10 (12.3%)	4 (14.3%)	<.01
Mortality by day 30	225 (37.1%)	14 (17.3%)	4 (14.3%)	<.001
Mortality by week 18	287 (47.3%)	25 (30.9%)	4 (14.3%)	<.001

Data are presented as n (%).
Abbreviation: IRIS, immune reconstitution inflammatory syndrome.

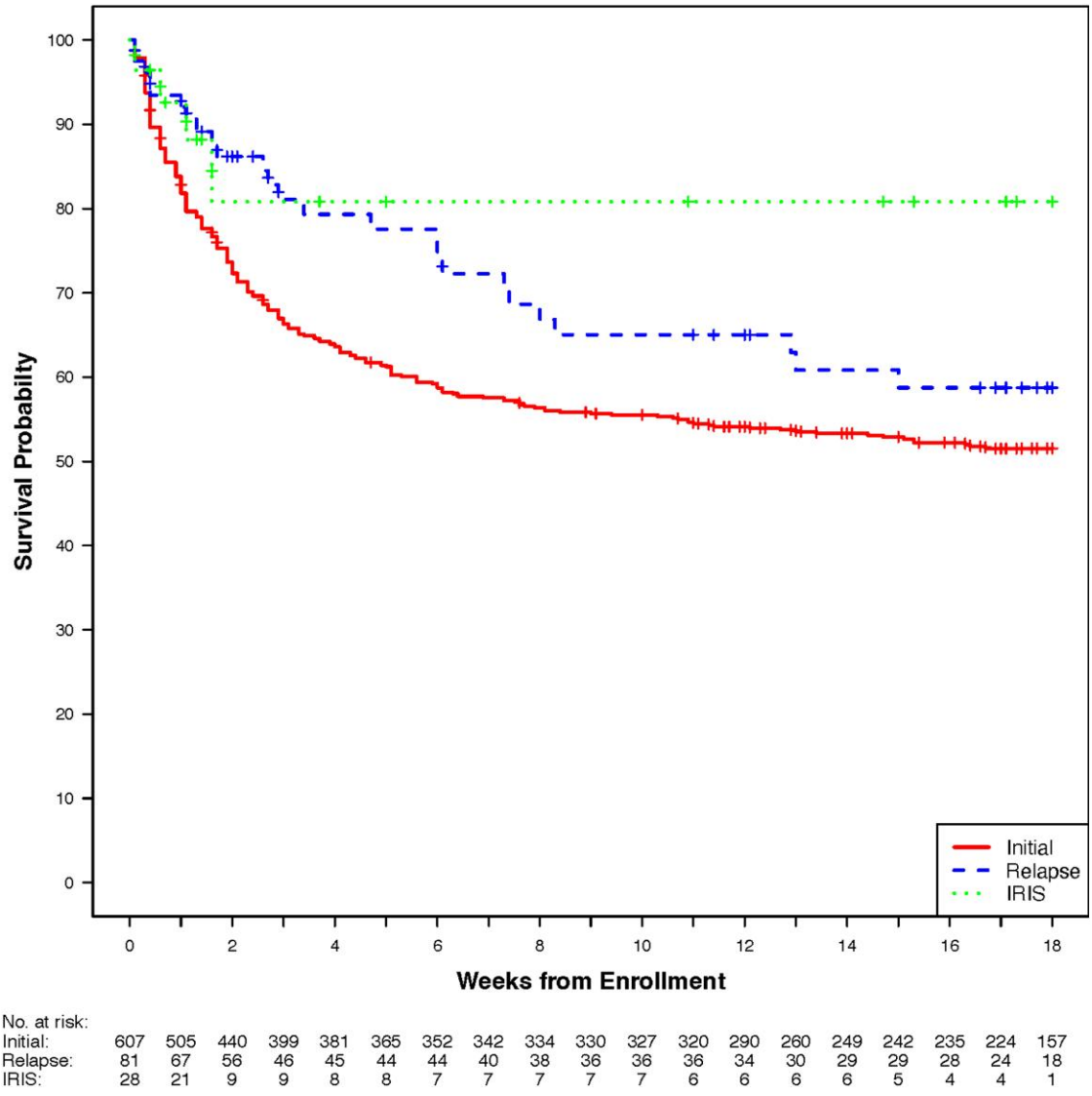

Figure 2. Kaplan-Meier curves for mortality over time among those with primary-episode cryptococcal meningitis, relapse of cryptococcal meningitis, and IRIS related to cryptococcal meningitis.

(100%) and relapse (90.1%), much higher than primary-episode cryptococcal meningitis (47.2%). Second-line ART use was also higher in relapse (28.6%) or IRIS (33.3%) compared with primary episodes (11.7%). Median CD4 counts were higher in IRIS compared with relapse as would be expected, although with some overlap. Thus, while a high CD4 count (>100 cells/μL) makes IRIS more likely than relapse, it is not definitive. Similarly, although *P* values were not less than .05 in direct statistical comparisons; time from HIV diagnosis and frequency of second-line ART use were numerically higher in IRIS compared with relapse. A larger dataset may be useful in determining whether these factors truly differ; however, one may reasonably posit that higher second-line ART use could be expected in IRIS given that a switch to a second-line regimen (from an ineffective regimen) would be predicted to cause immune reconstitution. This finding combined with a longer duration of diagnosis may mean higher CD4 counts at diagnosis and/or a longer duration of viral suppression prior to nonadherence to ART; however, this is conjecture and neither second-line ART nor duration from diagnosis alone should be used to differentiate IRIS and relapse based on our findings. Importantly, the inclusion of "change in ART regimen" in the definition of paradoxical IRIS may have affected the second-line ART variable.

Li and colleagues [19] recently reported that 25% (87/348) of their cohort of patients with HIV-associated cryptococcal meningitis experience relapse. Only 102 total patients (relapse: n = 49; primary episode: n = 53) had sufficient data for analysis, wherein they noted that CD4 counts of less than 20 cells/μL,

previous ART experience, and fewer than 4 weeks from symptom onset to presentation were all statistically associated with the occurrence of relapse in multivariate logistic regression. Notably, most ART-experienced patients in that study had not been regularly receiving ART at the time of diagnosis.

Unfortunately, given that only 29% (45/154) of those with prior episodes of cryptococcal meningitis reported prior fluconazole use (we would have expected near 100% prior usage), our findings related to prior antifungal use should be interpreted cautiously.

Median CSF WBC count was higher in those with IRIS (45 cell/μL; IQR: 8–128) compared with relapse (median: 4 cells/μL; IQR: 4–85), similar to a previous study (relapse, n = 5; IRIS, n = 33) in Kampala, reaffirming that, although an elevated CSF WBC count in this situation should raise one's suspicion for IRIS, it is not confirmatory [17]. Twenty-five percent (7/28) of participants with paradoxical IRIS in our cohort had CSF WBC counts of less than 5 cells/μL.

Interestingly, ICP was higher in those with relapse than those with primary cryptococcal meningitis despite lower quantitative culture results in those with relapse. We hypothesize that a combination of residual cryptococcal capsule in the CSF from prior meningitis with existing fibrosis/stenosis of arachnoid granulations may further impair CSF resorption.

As noted by others, CSF CrAg was not helpful in differentiating IRIS from relapse; and although culture effectively distinguishes them, the 7–14-day delay leads to indecisive care and/or empiric use of toxic antifungal therapies [3]. Results from mNGS and multiplex PCR, although limited in number, did reaffirm the accuracy of our adjudications. They also emphasized the possibility of multiple concurrent infections seen in those with advanced HIV, as well as the imperfect accuracy of the multiplex PCR in comparison to CSF CrAg for cryptococcal meningitis [20].

Li and colleagues [19] also reported 21.7% mortality among 46 patients with relapse (the survival time was cumulative from the first patient's presentation and not a single time point). Our findings interestingly showed similar early mortality among those with IRIS (14.3%) and relapse (12.3%) at day 14. However, by 18 weeks, IRIS mortality had not changed while mortality in those with relapse had increased to 30.9%. In fact, relapse mortality quickly surpasses IRIS at around week 4. This dynamic may reflect a decreased risk of other opportunistic infections in those with IRIS due to immune reconstitution compared with those with relapse, who often did not show signs of immune reconstitution.

We present well-characterized populations from a large cohort of patients with adjudicated presentations of recurrent symptoms after improvement from primary cryptococcal meningitis. Our findings give insights into potential differences in the era of widely available ART in Uganda, including factors that may have some utility in altering clinical decisions regarding symptom recurrence as either IRIS or relapse. Weaknesses include incomplete data for some variables, small numbers in the elevated ICP and persistent-symptoms groups, and limited selection by convenience of some tests (mNGS, glucose, and multiplex PCR). This study included patients from a clinical trial and a continuation cohort, which may introduce confounders by trial design. Further, our studies only included persons with cryptococcal meningitis, although other opportunistic pathogens can present similarly. Additional limitations include unaccounted-for confounding variables that may affect mortality such as antifungal adherence, ART adherence, frequency of LP, and treatment of IRIS. Last, we were not able to include data on fluconazole resistance, although this is uncommon when amphotericin induction is used, as was the case for all of our participants [5].

CONCLUSIONS

We present a large cohort of patients with various presentations of recurrent symptoms of cryptococcal meningitis and controls with primary episodes. We found that CSF WBC and blood CD4 counts were imperfect markers of possible IRIS compared with relapse and require additional confirmation. Additionally, we found higher mortality after the initial month in relapse compared with IRIS. This reinforces that, if those with IRIS can survive hospitalization and continue immune reconstitution, they have a good chance at improved outcomes as compared with those with relapse, often due to continued severe immune suppression.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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