

# A 12-Year-Old Tanzanian Boy With Headache: A Case Report

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## Case Report

A 12-year-old boy presented to the Kilimanjaro Christian Medical Centre (KCMC) referral hospital in Moshi, Tanzania, with complaints of 8 days of headache associated with photophobia, neck pain, and vomiting (Figure 1). Eleven weeks earlier, he was admitted at the regional government hospital for similar complaints when he was diagnosed with HIV and treated presumptively (cerebral spinal fluid [CSF] evaluation negative; Table 1) for cryptococcal meningitis (CM) initially with 800 mg intravenous (IV) fluconazole (induction therapy) then transitioned to oral 400 mg (consolidation therapy) according to Tanzanian National Guidelines.<sup>1</sup> Cryptococcal antigen (CrAg) lateral flow assay (LFA) was unavailable. He also received trimethoprim/sulfamethoxazole prophylaxis and IV ceftriaxone for possible bacterial meningitis. Three weeks after CM treatment, his clinical status improved and he began antiretroviral therapy (ART) with abacavir, lamivudine, and efavirenz. One month after starting ART and receiving fluconazole consolidation therapy, this patient reported no vomiting, resolution of his headache, and weight gain. Seven weeks after starting ART, he had a relapse of his original presenting symptoms (headache and vomiting) leading to presentation at KCMC.

## Hospital Course

At KCMC, he was slightly tachypneic (respiratory rate = 28 breaths/min), normocardic (heart rate = 87 beats/min), afebrile (temperature = 36.2°C), with an oxygen saturation of 99%. He was severely malnourished (weight = 23 kg; height = 136 cm; body mass index = 12.4 kg/m<sup>2</sup>; Z = -3) and had a deduced Glasgow Coma Score of 14. He had a positive Kerning's and Brudzinski's sign, papilledema, and mild ataxia. CSF analysis demonstrated a white blood cell count of  $6 \times 10^6$  cells/L, no organisms on gram stain, and India Ink and CSF CrAg were positive. Urea and creatinine measurements

remained unremarkable throughout admission. He received IV fluconazole (240 mg) daily until discharge, prophylactic trimethoprim/sulfamethoxazole, and continuation of his ART. Therapeutic lumbar punctures removing 15 to 25 cc of fluid were performed weekly. Opening pressure was not documented, but was noted to be "high" in one of the procedure notes. The therapeutic lumbar punctures offered relief for a few days, but symptoms of severe headache quickly returned. Acetazolamide was started to reduce intracranial pressure and daily prednisone was initiated for presumed immune reconstitution inflammatory syndrome (IRIS). His CD4 level was not available at the time of KCMC admission, but prior to initiating ART he had a CD4 count of 65 cells/ $\mu$ L. At this admission, his viral load was fully suppressed (HIV RNA <20 copies/mL). Once stabilized, he was discharged home with CM consolidation therapy (fluconazole 400 mg daily), ART, and an oral prednisone taper.

One week after discharge, he was readmitted to KCMC with similar complaints of headache and vomiting. Fundoscopy showed papilledema. CSF was CrAg-positive and Gene Xpert was negative for tuberculosis. After 2 weeks, his clinical condition still had not improved, so IV amphotericin B was added to his fluconazole regimen while his steroids were tapered. Despite escalation in management, his condition continued to deteriorate and he died soon after.

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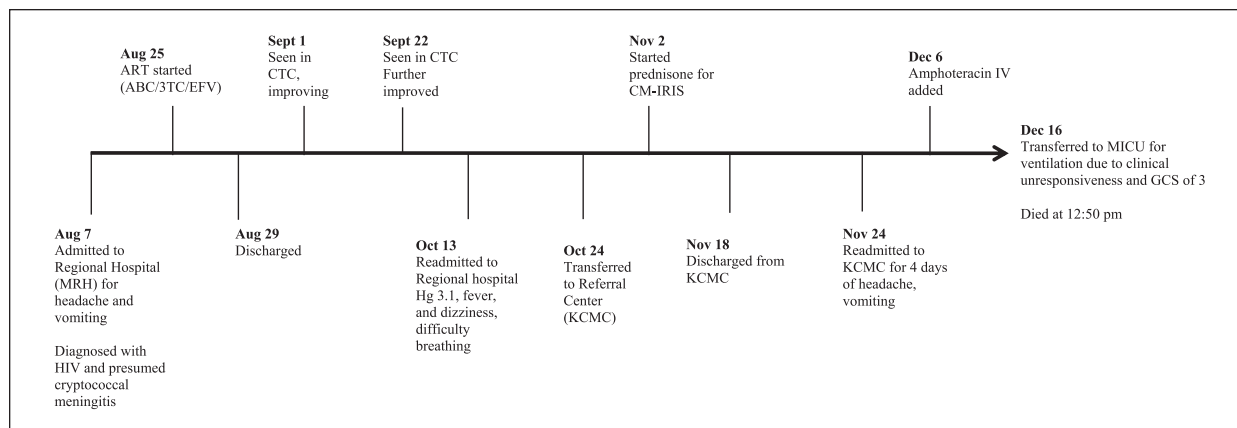
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**Figure 1.** Clinical timeline of events.

Abbreviations: ABC, abacavir; 3TC, lamivudine; EFV, efavirenz; CTC, Care and Treatment Clinic specific for HIV care; Hg, hemoglobin; IRIS, immune reconstitution inflammatory syndrome.

## Final Diagnosis

Paradoxical cryptococcal meningitis immune reconstitution inflammatory syndrome (CM-IRIS).

## Discussion

*Cryptococcus neoformans* is a common cause of meningoencephalitis among adolescents and adults with active HIV disease, but for unclear reasons is rare in children. The presumed low incidence of pediatric CM makes specific management challenging and treatment is based on adult studies.<sup>2</sup> The Tanzanian Treatment Guidelines state first-line CM therapy should include amphotericin B and flucytosine, but due to inaccessibility and cost, fluconazole monotherapy is offered as an alternative option in this setting.<sup>1</sup> Though amphotericin was secured late in the course, flucytosine was never available. Recent literature suggests that the addition of flucytosine to fluconazole may be noninferior to the standard recommendation of IV amphotericin plus flucytosine induction regimen.<sup>3</sup>

Decisions around when to begin ART in the face of CM in children is also a challenge. Current practice extrapolates from the adult setting, which supports delaying ART initiation for 5 weeks from diagnosis and treatment of CM as compared with early ART initiation after 1 to 2 weeks because of increased risk of mortality and greater risk of IRIS.<sup>4</sup> Risk factors for IRIS include low CD4 count, advanced clinical stage, and coexisting infection,<sup>4</sup> all of which were present in this child. If CM-IRIS occurs, as in this case, management remains elusive. CM-IRIS is defined in 2 ways: unmasking, when subclinical disease displays symptoms shortly after starting ART; and paradoxical, when a period of clinical improvement is followed by rebound worsening after beginning ART.<sup>5</sup> No clinical trials have specifically investigated treatment for

CM-IRIS. Anti-inflammatory measures to dampen the exaggerated inflammatory response might help,<sup>6</sup> but this can be dangerous when co-infections are present. A recent randomized controlled trial among adults with HIV and CM suggested that dexamethasone may increase risk of mortality and should be avoided; however, the study was not powered to evaluate its use in CM-IRIS.<sup>7</sup>

Management issues in low-resource settings raise the question whether children newly diagnosed with HIV should be screened for cryptococcal disease, a practice shown to reduce unmasking infections.<sup>6</sup> Screening CrAg LFA or enzyme immunoassay reflex testing may be useful, especially when the CD4 count is less than 100 cells/ $\mu$ L, but is often unavailable in low-resource settings. CrAg is rarely utilized in pediatrics, though with relatively low cost (\$2/test) and excellent sensitivity (99%) and specificity (99%) in adults,<sup>8</sup> use in high-risk pediatric cases may be life-saving.

## Conclusion

The risk of CM-IRIS in pediatric patients with HIV following initiation of ART remains a relevant threat to mortality. The timing of ART initiation is crucial, yet data are lacking in the pediatric population. With the availability of screening tools, like CrAg LFA, every child suspected based on symptoms or with a CD4 count of 100 cell/ $\mu$ L or fewer should be screened. If positive, ART treatment should be delayed until CM infection is treated to minimize the risk of IRIS. The accessibility of first-line antifungal agents, amphotericin B and flucytosine, at an affordable price is also urgently needed in resource-limited settings that carry the highest burden of disease.<sup>9</sup> Further study is needed regarding the pediatric CM burden and to confirm treatment guidelines in this unique population. With

**Table 1.** Summary of Pertinent Laboratory Results.

Dates	Test	Result	
<i>Mawenzi</i>			
August 7-29, 2016; initial presentation	HIV antibody (Bioline and Unigold)	Reactive	
	CD4	65 cells/ $\mu$ L	
	Malaria (rapid)	Negative	
	CSF traumatic	Macro: blood stained Micro: RBC+++ Gram stain: no organisms seen	
	CSF India Ink	Negative	
	Hepatitis A, B, and C antigens	Negative	
	Hemoglobin	11.9 g/dL	
	ALT	14 (ref = 0-40)	
	AST	74 (ref = 0-40)	
	<i>Brucella</i>	Negative	
	Chest X-ray	Parent report: negative	
	October 13-24, 2016; readmission	Hemoglobin <sup>a</sup>	3.1 g/dL
		Abdominal ultrasound	Mild hepatomegaly (15.2 cm), no hepatoma, normal liver texture, and no masses; spleen and kidneys normal
<i>Kilimanjaro Christian Medical Centre</i>			
October 24 to November 18, 2016; transferred from Mawenzi for admission	Malaria (rapid)	Negative	
	Hemoglobin <sup>a</sup>	5.7 g/dL	
	ALT	12 (ref = 0-40)	
	AST	16 (ref = 0-40)	
	Brain CT	Single, oval, homogeneous, hyperdense lesion left parietal region 2 $\times$ 4.9 $\times$ 4.4 mm with enlarged lateral ventricles	
	CSF protein	0.616 g/L	
	CSF glucose	3.29 $\mu$ mol/L	
	CSF WBC	600 000	
	CSF gram stain	No organisms seen	
	CSF India Ink	Positive	
	CSF cryptococcal antigen	Positive	
	Toxoplasmosis	Negative	
	Hepatitis B surface antigen	Negative	
	Chest X-ray	Negative	
	Sodium (November 1, 2016)	126 $\mu$ mol/L (ref = 136-145)	
	Viral load (November 18, 2016)	<20 copies/mL	
	November 24 to December 16, 2016; readmission	Hemoglobin <sup>a</sup>	5.8 g/dL (ref = 11-13)
Sodium (December 9, 2016)		131 $\mu$ mol/L (136-145)	
Sodium (December 15, 2016)		125 $\mu$ mol/L (136-145)	

Abbreviations: HIV, human immunodeficiency virus; CSF, cerebral spinal fluid; RBC, red blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; WBC, white blood cell.

<sup>a</sup>Two units of packed RBCs transfused.

ART scale-up, initiatives like the UNAIDS 90-90-90 targets, screening of vulnerable children to help guide timing of ART initiation is needed now more than ever.

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### Author Contributions

AR: Contributed to conception and design; contributed to analysis; drafted the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

AM: Contributed to conception and design; contributed to analysis; drafted the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

ZT: Contributed to conception and design; contributed to analysis; drafted the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

GK: Contributed to analysis; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

DD: Contributed to conception and design; contributed to analysis; drafted the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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### Informed Consent

Written informed consent was not able to be obtained from the patient's guardians for the publication of this case report. Over several months, multiple attempts were made to contact the family of the deceased patient, but they were unreachable. We have anonymized the details of the case to protect patient and family privacy. Additionally, the unfortunate high incidence of this infection further anonymizes this individual patient. We believe we have written the case in such a way as to protect the privacy and dignity of the patient and his family.

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### References

1. United Republic of Tanzania Ministry of Health and Social Welfare; National AIDS Control Programme. National guidelines for the management of HIV and AIDS. [https://aidsfree.usaid.gov/sites/default/files/04\\_11\\_2016.tanzania\\_national\\_guideline\\_for\\_management\\_hiv\\_and\\_aids\\_may\\_2015\\_tagged.pdf](https://aidsfree.usaid.gov/sites/default/files/04_11_2016.tanzania_national_guideline_for_management_hiv_and_aids_may_2015_tagged.pdf). Published May 2015. Accessed January 3, 2018.
2. Meiring ST, Quan VC, Cohen C, et al; Group for Enteric, Respiratory, Meningeal Disease Surveillance in South Africa. A comparison of cases of paediatric-onset and adult-onset cryptococcosis detected through population-based surveillance, 2005-2007. *AIDS*. 2012;26:2307-2314.
3. Molloy SF, Kanyama C, Heyderman RS, et al; ACTA Trial Study Team. Antifungal combinations for treatment of cryptococcal meningitis in Africa. *N Engl J Med*. 2018;378:1004-1017.
4. Boulware DR, Meya DB, Muzoora C, et al; COAT Trial Team. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N Engl J Med*. 2014;370:2487-2498.
5. Haddow LJ, Colebunders R, Meintjes G, et al; International Network for the Study of HIV-Associated IRIS. Cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected individuals: proposed clinical case definitions. *Lancet Infect Dis*. 2010;10:791-802.
6. Boulware DR, Callens S, Pahwa S. Pediatric HIV immune reconstitution inflammatory syndrome (IRIS). *Curr Opin HIV AIDS*. 2008;3:461-467.
7. Beardsley J, Wolbers M, Kibengo FM, et al; CryptoDex Investigators. Adjunctive dexamethasone in HIV-associated cryptococcal meningitis. *N Engl J Med*. 2016;374:542-554.
8. Boulware DR, Rolfes MA, Rajasingham R, et al. Multisite validation of cryptococcal antigen lateral flow assay and quantification by laser thermal contrast. *Emerg Infect Dis*. 2014;20:45.
9. Loyse A, Thangaraj H, Easterbrook P, et al. Cryptococcal meningitis: improving access to essential antifungal medicines in resource-poor countries. *Lancet Infect Dis*. 2013;13:629-637.