Hearing Loss after Discontinuing Secondary Prophylaxis for Cryptococcal Meningitis: Relapse or Immune Reconstitution?

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Abstract

Relapse and immune reconstitution syndrome are difficult to distinguish in HIV-infected patients treated with antiretroviral therapy (ART). We report on a 26-year-old HIV-infected male (CDC C3) with hearing loss on the right side 2 months after discontinuing secondary prophylaxis for cryptococcal meningitis. CD4 cell counts had increased from 32/µl to stable counts > 200/µl for the preceding 6 months on ART but HIV replication was not fully suppressed (7,000 copies/ml). Magnetic resonance imaging identified lesions at the origin of the right cranial nerve VIII. Lumbar puncture revealed monocytic pleocytosis, slightly increased protein, but normal glucose and lactate levels, negative microbiological studies. Fluconazole was restarted and a new ART regimen was started in order to fully suppress HIV replication. Clinical and radiological signs were reversible during follow-up, and secondary prophylaxis was stopped after 6 months without adverse events. We review 26 published cases of cryptococcal infections with immune reconstitution syndrome and highlight the distinguishing features.

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Introduction

The discontinuation of secondary prophylaxis for cryptococcal meningitis is considered safe in HIV-infected patients on highly active antiretroviral therapy (ART) with stable CD4 cell counts > 100 cells/µl. This is supported by data from prospective studies [1], cohort studies [2] and summarized in current guidelines [3]. However, despite clinical success and improved CD4 counts, paradoxical worsening of the clinical condition has been observed in some cases. The differential diagnosis includes relapse or immune reconstitution syndrome, which are difficult to distinguish from one another [4, 5].

Case Report

A 26-year-old male from Thailand presented with headache and fever to our outpatient department. Cryptococcal meningitis and pneumonia was diagnosed as well as HIV-1 infection CDC C3 (CD4 cell counts of 32/µl; HIV viral load of 89,000 copies/ml [4.9 log 10]). *Cryptococcus neoformans* antigen was positive in blood (1:1,024). Computer scan of the neurocranium was unremarkable. In the cerebrospinal fluid (CSF), pleocytosis with 507/µl polymorphs, elevated lactate (3.4 mmol/l), elevated protein (747 mg/l) and *C. neoformans* was identified by culture. The patient was treated with amphotericin-B and flucytosine. The clinical condition improved, and antigen titers decreased. Secondary prophylaxis with fluconazole 400 mg daily was administered as well as trimethoprim/sulfamethoxazole (TMP/SMX) three times weekly as primary prophylaxis for *Pneumocystis carinii (jiroveci)*. ART was initiated consisting of stavudine, lamivudine and nelfinavir (Figure 1A). The HIV-RNA viral load decreased by 2 log 10 and CD4 cell counts increased to 234/µl over the following 6 months. However, HIV replication was sub-optimally suppressed with viral loads around 2,000 copies/ml. ART was switched to didanosine, lamivudine and nevirapine but without significant improvement. After 9 months of stable CD4 cell counts above 200/µl, secondary prophylaxis with fluconazole was stopped (Figure 1A). Two months later, the patient presented with sudden hearing loss on the right side. The clinical examination was otherwise unremarkable and there was no evidence of vertigo. The audiogramm revealed right-sided central hearing loss at 1,000 Hz. Magnetic resonance imaging of the brain showed multiple small

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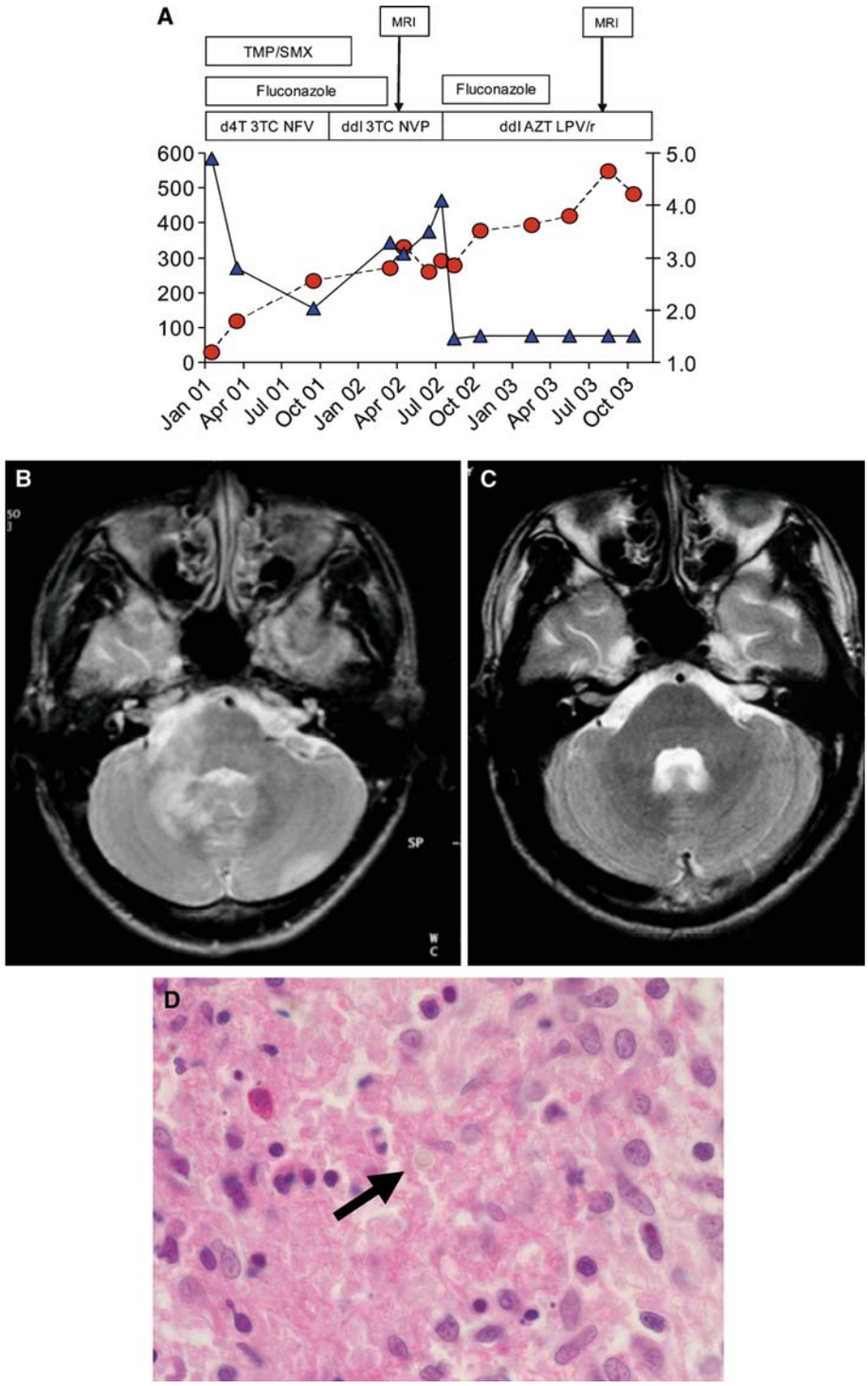

Figure 1. A) Time course of HIV surrogate markers (CD4 cell counts, circles, left axis; HIV viral load in log 10, triangels, right axis), drug treatment in boxes (stavudine, d4T; lamivudine, 3TC; zidovudine, AZT; nelfinavir, NFV; didanosine, DDI; nevirapine, NVP; lopinavir/ritonavir, LPV/r) and MRI in boxes. **B**) T2-weighted MRI of the head at diagnosis showing hyperintense lesion with edema in the right cerebellum and in the brain stem near the meatus acusticus internus. **C**) T2-weighted MRI of the head 9 months later showing dissolved lesion and edema in the right cerebellum and in the brain stem near the meatus acusticus internus. **D**) Lymph node histology showing granuloma with *Cryptococcus neoformans* (culture negative, antigen positive).

contrast enhancing lesions with edema in the left and right cortex and a major lesion in the right cerebellum near the root of the eighth cranial nerve which also emerged in T2 weigted imaging (Figure 1B). In the CSF, monocytic pleocytosis (16/µl), low lactate (1.3 mmol/l), low glucose (2.9 mmol/l) and normal protein levels (480 mg/l) were detected. Bacterial and fungal culture remained negative. Also, negative results were obtained for cryptococcal antigen, cysticercosis antibodies, and PCR studies specific for *M. tuberculosis*, cytomegalovirus, polyomavirus JC, Toxoplasma gondii, and Epstein-Barr virus. The differential diagnosis included relapsing cryptococcal infection or immune reconstitution syndrome. Fluconazole was restarted (400 mg/day). HIV resistance testing was performed and ART was changed accordingly to zidovudine, didanosine and lopinavir/ritonavir. The HIV-RNA viral load dropped under the detection limit (Figure 1A). Six weeks later, hearing loss was unchanged, but painful cervical lymphadenopathy developed. Biopsy of a cervical lymph node showed granulomas with cryptococci (Figure 1D). Cultures from lymph tissue remained negative, but *Cryptococcus* antigen was detectable in lymph node extracts. After 3 months, hearing improved and decreasing lesion intensity was noted in the MRI (Figure 1C). After 12 months, the CD4 cell counts measured 392/µl and the HIV-RNA viral load remained < 50 copies/ml. Fluconazole was discontinued and no signs of relapse occurred during a follow-up of 30 months. Audiogram confirmed a near complete recovery.

Discussion

Central neurological symptoms (central hearing loss) and extensive MRI lesions were unexpected in view of adequate antimicrobial therapy and stable CD4 cell counts above 200/µL for more than 6 months. Although we could not diagnose ongoing cryptococcal disease, relapse had to be considered. On the other hand, CSF pleocytosis and contrast enhancement in MRI rendered immune reconstitution

Table 1
Review of published cases with cryptococcal infections and IRS after initiation of highly active antiretroviral therapy. Table includes CD4 count and HIV load before initiation HAART, initial symptoms of cryptococcal infection, time from infection to HAART, CD4 count and HIV load at diagnosis of IRS, symptoms of IRS, time from HAART to IRS, HAART regimen and treatment of IRS.

Patient [and references]	CD4 count (cells/µl)	HIV load (copies/ml)	Inital symptoms of cryptococcal infection	Time from infection to HAART (months)	CD4 count (cells/µl)	HIV load (copies/ml)	Symptoms of IRS	Time from HAART to IRS (months)	HAART regimen	Treatment
1 [7]	25	556,000	Meningitis and elevated ICP[b]	1	66	< 400	Hilar lymphadenopathy and hypercalcemia	2	SQV, RTV, 3TC, AZT	Secondary prophylaxis with fluconazole
2 [7]	39	534,000	Pulmonary nodules	2	57	500	Pulmonary infiltrates with cavitations	2	EFV, 3TC, d4T	Unknown
3 [7]	102	> 750,000	Cryptococcemia	0	231	< 50	Supraclavicular granulomatous mass	11	SQV, RTV,3TC, d4T	Partial surgical excision, AmB[a], fluconazole 400 mg
4 [7]	10	45,496	Meningitis and elevated ICP[b]	2	223	< 50	Aseptic meningitis and elevated ICP[b]	4	EFV, ABC, 3TC	Serial lumbar punctures, AmB[a], fluconazole 400 mg
5 (7)	47	224,000	Meningitis and elevated ICP[b]	1	306	< 50	Aseptic meningitis and elevated ICP[b]	10	EFV, AZT, 3TC	Serial lumbar punctures, AmB[a], fluconazole 400 mg
6 [8]	120	936,000	Fever and Cryptococcemia	1	200	< 40	Supraclavicular, mediastinal lymphadenopathy fever	5	IDV, 3TC, d4T	Fluconazole 400 mg
7 [8]	17	1,000,000	Meningitis	1	48	< 40	Aseptic meningitis, mediastinal lymphadenopathy	3	IDV, 3TC, d4T	AmB[a], flucytosine, Fluconazole 400 mg
8 [8]	64	1,000,000	Meningitis	1	329	< 40	Laterocervical and left axillary lymphadenopathy, fever	2	IDV, 3TC, d4T	Liposomal AmB[a], Fluconazole 400 mg, surgery
9 [5]	40	70,000	Meningitis	1	240	60	Aseptic meningitis	0.5	SQV 3TC, AZT	Fluconazole 400 mg
10 [9]	17	375,000	Meningitis	1	220	< 40	Cerebral cryptococcomas, aseptic meningitis	7	NFV, AZT, 3TC	Liposomal, AmB[a], Fluconazole 400 mg
11 [9]	27	108,574	Meningitis	0	205	< 40	Cerebral cryptococcomas, aseptic meningitis	6	NFV, AZT, 3TC	Liposomal AmB[a], Fluconazole 400 mg
12 [10]	16	110,000	Meningitis, abducens paralysis	1	38	166	Cerebral cryptococcomas, aseptic meningitis	1	3TC, AZT, LPV/RIT	Fluconazole 400 mg, Methylprednisolon, hydroxychloroquine, ART discontinued

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Table 1 **(continued)**

Patient [and references]	CD4 count (cells/µl)	HIV load (copies/ml)	Inital symptoms of cryptococcal infection	Time from infection to HAART (months)	CD4 count (cells/µl)	HIV load (copies/ml)	Symptoms of IRS	Time from HAART to IRS (months)	HAART regimen	Treatment
13 [11]	3	Unknown	Disseminated and meningitis and cryptococcomas	Unclear	640	Undetectable	Intramedullary abcess Supraclavicular, mediastinal lymphadenopathy	34	IDV, 3TC, d4T	Surgical excision, AmB[a], flucytosine Fluconazole 400 mg
14 [12]	41	> 750,000	Meningitis, abducens paralysis	1	44	< 400	Meningitis	1	AZT, 3TC, NFC	AmB[a], Fluconazole 400 mg, dexamethasone
15 [13]	6	430,000	Meningitis, lymphadenopathy	12	63	5,500	Lymphadenopathy	8	IDV, 3TC, d4T	AmB[a], NSAID
16 [13]	28	430,000	Meningitis	1	259	6,500	Cervical necrotic lymphadenopathy, retropharyngeal abscess	14	Unknown	AmB[a], Methylprednisolon
17 [14]	38	75,600	Pulmonary lesion	Unclear	54	344	Pulmonary lesion doubled in size	1	D4T, 3TC, NFV	AmB[a], Fluconazole 300 mg
18 [15]	3	Unknown	Meningitis	2–23	485	< 400	Intracranial cryptococcoma	24–36	Unknown	None
19 [16]	67	650,000	Meningitis	1	370	537	Meningitis, elevated ICPb	1	D4T, 3TC, NVP	None
20 [17]	Unknown	Unknown	Meningitis	36	137	< 500	Mediastinal lymphadenitis	6	AZT, 3TC, IDV	Unchanged Fluconazole 400 mg
21 [17]	Unknown	Unknown	None	–	110	6,000	Mediastinal lymphadenitis	–	D4T, 3TC, NFV	AmB[a]
22 [18]	7	78,000	Cryptococcemia	18	186	< 40	Cervical lymphadenitis	3	D4T, 3TC, NFV	NSAID
23 [19]	1	141,463	Meningitis, cervical adenopathy	1–2	409	788	Lymphadenopathy	18	D4T, 3TC, NFV	AmB[a], Fluconazole 800 mg
24 [19]	4	52,047	Meningitis, mediastinal lymphadenitis	13	209	121	Meningitis	2	Unknown	AmB[a], Fluconazole 800 mg
25 [19]	4	52,047	Meningitis, mediastinal lymphadenitis	13	231	93	Cervical lymphadenopathy	8	Unknown	Already under Fluconazole 800 mg
26 [19]	1	501,538	Meningitis	6	180	< 400	Lymphadenopathy	9	D4T, 3TC, EFA	Unknown

[a] AmB: amphotericin-B; [b] ICP: intracranial pressure

syndrome another likely diagnosis. The subsequent onset of granulomatous lymphadenitis with non-viable *C. neoformans* also supported this hypothesis, but the long time of onset of more than 6 months after starting ART is unusual. In the literature, variable durations of 5 days to 34 months have been reported with increases in CD4 cell counts ranging from 3 to 637/µl (Table 1 [5, 7–19]). In some cases, IRS may in fact unmask hitherto undiagnosed cryptococcosis [5]. Table 1 lists 26 published cases with cryptococcal infections that developed an IRS after initiation of highly active antiretroviral therapy [5, 7–19]. At the time when IRS developed the CD4 count increased in 21 patients > twofold and viral load decreased > 2log 10 copies/ml. Similar to our case, cryptococcal relapse could not be excluded in 20 patients who were therefore treated with antifungal therapy (Amphothericin B or high dose fluconazole) and secondary prophylaxis. In five patients, inflammatory treatment with steroids or non steroidal anti-inflammatory drugs was administered. All patients recovered from IRS. No significant correlation between initial signs and symptoms and the subsequent manifestation of IRS are apparent.

IRS occurs in 10–30% of patients treated with ART and is associated a variety of microbial and non-microbial antigens. Often, initial CD4 cell counts are very low and briskly increase after starting ART [4]. Mycobacterial and cryptococcal antigens are frequently implicated in IRS. Indeed, a recent study found C. neoformans-related IRS in 30% of HIV-patients [6]. Compared to patients without IRS, patients with *C. neoformans*-related IRS had a lower HIV viral load, higher CD4 cell count, a higher CSF-opening pressure, higher mononuclear pleocytosis and lower cryptococcal antigen titer in the CSF. However, clinical signs and symptoms were not specific. Antifungal treatment was administered in all cases which emphasizes the clinical dilemma of suspected relapse versus IRS. Of note, neither relapse nor immune reconstitution was reported in a recent prospective study [1]. All patients in this study had optimally suppressed HIV viral loads of < 50 copies/ml. One may speculate whether sub-optimally suppressed HIV replication in our patient may have preferentially infected and hence, deleted the *Cryptococcus*-specific CD4 cells which were activated by abundant antigen. The hypothesis may account for a true relapse despite CD4 cell counts > 200/µl and may explain the initial signs and symptoms in our patient. Possibly, discontinuation of secondary prophylaxis may bear a higher risk in sub-optimally suppressed HIV-patients.

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