CASE REPORT

Late onset of cryptococcal cervical lymphadenitis following immune reconstitution inflammatory syndrome in a patient with AIDS

Meenakshi Sethupathi,¹ Kathir Yoganathan²

¹Department of GUM/HIV, Betsi Cadwaladr University Health Board, Bangor, UK
²Department of Genito-Urinary and HIV Medicine, Abertawe Bro Morgannwg University Health Board, Singleton Hospital, Swansea, South Wales, UK

Correspondence to

Dr Kathir Yoganathan,
 kathir.yoganathan@wales.nhs.uk

Accepted 14 December 2014

SUMMARY

A 32-year-old woman was diagnosed HIV positive with disseminated cryptococcal infection in May 2006. Her initial CD4 was 7 cells/ μ L and she had a right supraclavicular nodal mass, which was biopsied and shown to be consistent with cryptococcal lymphadenitis. She was treated for disseminated cryptococcal infection and was started on antiretroviral medications subsequently. Two years later, she developed a left supraclavicular mass. Her CD4 count was 320 cells/ μ L and HIV RNA level was undetectable. Investigations and biopsy results were consistent with a late presentation of cryptococcal immune reconstitution inflammatory syndrome (IRIS). She was treated with oral corticosteroids and her symptoms resolved completely. IRIS is a recognised complication of HIV treatment and occurs in a significant percentage of patients within the first 3 months of starting antiretroviral therapy. This case report illustrates the importance of recognising late presentations of IRIS. It is vital to differentiate true cryptococcal lymphadenitis from IRIS-induced cryptococcal lymphadenitis.

BACKGROUND

Restoration of immunity in some profoundly immunosuppressed patients after effective antiretroviral therapy (ART) can lead to a pathological inflammatory response and paradoxical worsening of clinical presentation. This complication, known as immune reconstitution inflammatory syndrome (IRIS), commonly occurs as a result of restored immunity to specific infectious agents, such as mycobacteria, *Cryptococcus*, herpes zoster, viral hepatitis and cytomegalovirus infections. The majority of IRIS presentations occur in the first 3 months after starting ART. We report a case of late onset of cryptococcal IRIS, presenting as necrotising inflammatory cervical lymphadenitis, 25 months following treatment for disseminated cryptococcal infection and 24 months after starting ART.

CASE PRESENTATION

A 32-year-old Thai woman was diagnosed with HIV infection in May 2006. Two days later, she was admitted with a history of cough, fever, night sweats, lethargy and a tender right supraclavicular mass. On examination, she had fever and had tender right supraclavicular lymph nodes measuring 3 cm $\times$ 2 cm. She did not have any evidence of meningitis clinically. Her initial CD4 count was 7 cells/ μ L and her highest viral load (HIV RNA) was

1.4 million copies/mL. Lymph node biopsy showed a granulomatous lymphadenitis consistent with fungal infection. Blood culture showed a growth of *Cryptococcus neoformans* and cryptococcal antigen (Cr Ag) titre was 1 in 400. She was treated with liposomal amphotericin B (3 mg/kg/day) for 2 weeks followed by fluconazole 400 mg daily for 6 months. ART with abacavir, lamivudine and boosted atazanavir was started in June 2006, 3 weeks after initial presentation. Her viral load dropped from 1.4 million to 347 copies 4 weeks after starting ART and the CD4 rose to 64 cells/ μ L. Her viral load was undetectable and her CD4 count was over 200 cells/ μ L 6 months after starting ART. Secondary prophylaxis with fluconazole was stopped when her CD4 was over 200 cells/ μ L.

In June 2008, the patient presented with a painless swelling in the left supraclavicular region (figure 1). Her CD4 count was 324 cells/ μ L and HIV RNA was less than 40 copies/mL. Examination showed non-tender firm left supraclavicular lymphadenopathy. No other lymph nodes were palpable. She had no history of weight loss or night sweats. Further investigations showed erythrocyte sedimentation rate of 41, C reactive protein of 3 mg/L and Cr Ag titre of 1 in 32. Fine-needle aspiration of the lymph node was inadequate for histology and negative for tuberculosis PCR. Histology of excision of lymph node showed a benign granulomatous inflammatory reaction. Macrophages within this contained elements that were Periodic acid-Schiff and Grocott positive. Morphological appearances were regarded as in keeping with *Cryptococcus*, but other fungal infections could not be excluded (figure 2). Culture of the tissue was negative for tuberculosis and fungal infection.

Figure 1 Enlarged left supraclavicular lymph nodes.

CrossMark

To cite: Sethupathi M, Yoganathan K. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-206601

Figure 2 Grocott stain showing benign granulomatous inflammatory reaction with morphological appearance of cryptococcal infection.

DIFFERENTIAL DIAGNOSIS

- ▶ Cryptococcal lymphadenitis due to cryptococcal infection
- ▶ Cryptococcal lymphadenitis due to IRIS
- ▶ Tuberculous lymphadenitis

TREATMENT

The patient was initially treated with fluconazole 400 mg daily along with non-steroidal anti-inflammatory medications. Her symptoms did not improve after 4 weeks and she developed non-tender lymphadenopathy in the right supraclavicular area. She was then treated with prednisolone 30 mg daily for 10 days. Her symptoms improved but the lymphadenopathy recurred when her prednisolone dose was reduced to 15 mg daily. She was therefore re-treated with prednisolone 30 mg a day; the dose was tapered slowly by 5 mg every 2 weeks for a total of 3 months. Her symptoms resolved completely.

OUTCOME AND FOLLOW-UP

The patient remains well on ART with a good CD4 count of 499 cells/ μ L and undetectable HIV RNA viral load. Her cervical lymphadenopathy has not recurred to date.

DISCUSSION

Restoration of immunity in patients with advanced HIV infection with effective ART can lead to a dysregulated immune response and paradoxical worsening of clinical presentation.¹ This complication, known as IRIS, commonly occurs as a result of restored immunity to specific infectious agents, such as mycobacterial, *Cryptococcus*, herpes zoster, viral hepatitis and cytomegalovirus infections.^{2,3} The antigenic stimuli in infectious agents are either intact viable or dead organisms or their residual antigens.⁴ The majority of IRIS presentations occur in the first 3 months after starting ART and the incidence of IRIS varies depending on the cohort and the specific infection that manifests. Disseminated infection with *C. neoformans* is a common life-threatening fungal infection in patients with advanced HIV infection. Cryptococcal IRIS (C IRIS) can occur in 6–45% of these patients, mostly in the first 2 months after starting ART.⁵

The incidence and timing of C IRIS appear to be very variable.^{6,7} The median time of onset of C IRIS varies from 1 to 10 months. However, it has been reported to present even 3 years after starting ART.^{8,9} C IRIS can present as paradoxical IRIS in patients who are diagnosed with cryptococcal infection and treated for it prior to starting ART. It can also present as unmasking IRIS in patients who develop symptoms of cryptococcosis after starting ART. The diagnosis of paradoxical IRIS in

our patient fits with the case definition for paradoxical cryptococcal IRIS in patients with HIV infection published by Haddow *et al*,⁸ except that in our patient it occurred later than the proposed time limit of 12 months after ART initiation. Our patient responded well clinically to cryptococcal treatment during her initial diagnosis. Two years after initiation of ART, lymphadenopathy recurred at a different site and all cultures including fungal were negative. Her Cr Ag titres were much lower than those at diagnosis of initial disseminated cryptococcal infection. Histology confirmed granulomatous fungal infection suggesting the possibility of delayed IRIS due to immune response against non-viable pathogens.^{4,10} Her CD4 counts remained over 300 cells/ μ L during her illness and her viral load remained less than 40 copies indicating that it was not due to failure of her ART or relapse of cryptococcal infection.

A recent literature review of risk factors for paradoxical C IRIS has shown that a low inflammatory response and low CD4 count at baseline, rapid restoration of immunity and high organism or antigen load at baseline and initiation of ART are associated with the risk of developing IRIS.^{5,11} Our patient did not undergo a lumbar puncture, as she did not have any clinical evidence of meningitis. High burden of organism at baseline shown by high fungemia and high Cr Ag titre contributed as another risk factor for the development of C IRIS in our patient. C IRIS is associated with significant mortality and morbidity so delayed manifestation presents a clinical dilemma in diagnosis and management of this condition.

The differentiation of C IRIS and relapse of *C. neoformans* infection is vital since the management and outcome of these conditions are different. The symptoms are often similar and cannot be differentiated based on clinical symptoms alone, but the culture is typically a distinguishing feature. In various studies, the majority of the clinical manifestations of IRIS resolved with continuation of ART and antifungal treatment. However, some required non-steroidal anti-inflammatory therapy and others, as was noted in our patient, needed a prolonged tapering course of systemic corticosteroid treatment. Our patient's lymphadenopathy relapsed after reducing the dose of corticosteroid rapidly. It is therefore essential for clinicians to recognise C IRIS in patients who have initially been treated for cryptococcal infection and to treat them with a prolonged course of steroid, if indicated, as was done with our patient.

Learning points

- ▶ The possibility of development of immune reconstitution inflammatory syndrome (IRIS) should be considered when ART is initiated in HIV patients, especially those with risk factors such as low CD4 counts, high organism burden, high serum cryptococcal antigen and poor initial inflammatory response.
- ▶ Although most patients develop IRIS within the first few months of starting antiretrovirals, a few patients can have a delayed presentation of IRIS, especially cryptococcal IRIS.
- ▶ Failure to recognise delayed onset of cryptococcal IRIS may lead to unnecessary investigations and delay in diagnosis.
- ▶ It is vital to differentiate lymphadenitis caused by ongoing cryptococcal infection from lymphadenitis caused by paradoxical IRIS.
- ▶ A prolonged course of steroids may be needed for the effective management of IRIS; and IRIS symptoms may recur as steroids are tapered.

Contributors Both authors managed this patient at Singleton Hospital and contributed in writing this case report.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Shelburne SA, Visnegarwala F, Darcourt J, *et al.* Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. *AIDS* 2005;19:399–406.
- Bopage R, Yoganathan K. CMV cholangiopathy in HIV infected man following HAART: Immune recovery inflammatory syndrome. *HIV Med* 2006;7:36.
- Skiest DJ, Hesser LJ, Hardy RD. Cryptococcal immune reconstitution inflammatory syndrome: report of four cases in three patients and review of the literature. *J Infect* 2005;51:289–97.
- Sharma SK, Soneja M. HIV & immune reconstitution inflammatory syndrome (IRIS). *Indian J Med Res* 2011;134:866–77.
- Longley N, Harrison TS, Jarvis JN. Cryptococcal immune reconstitution inflammatory syndrome. *Curr Opin Infect Dis* 2013;26:26–34.
- Murdoch DM, Venter WD, Van Rie A, *et al.* Immune reconstitution inflammatory syndrome (IRIS): review of common infectious manifestations and treatment options. *AIDS Res Ther* 2007;4:9.
- Somnuek S, Ubonvan J, Sasisopin K. Timing of cryptococcal immune reconstitution inflammatory syndrome after antiretroviral therapy in patients with AIDS and cryptococcal meningitis. *J Acquir Immune Defic Syndr* 2007;45:595–6.
- Haddow LJ, Colebunders R, Meintjes G, *et al.* Cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected individuals: proposed clinical case definitions. *Lancet Infect Dis* 2010;10:791–802.
- Rambeloarisoa J, Batisse D, Thiebaut JB, *et al.* Intramedullary abscess resulting from disseminated cryptococcosis despite immune restoration in a patient with AIDS. *J Infect* 2002;44:185–8.
- Murdoch DM, Venter WDF, Feldman C, *et al.* Incidence and risk factors for the immune reconstitution inflammatory syndrome in HIV patients in South Africa: a prospective study. *AIDS* 2008;22:601–10.
- Boulware DR, Bonham SC, Meya DB, *et al.* Paucity of initial cerebrospinal fluid inflammation in cryptococcal meningitis is associated with subsequent immune reconstitution inflammatory syndrome. *J Infect Dis* 2010;202:962–70.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow