CASE REPORT

Disseminated cryptococcosis in HIV negative patient

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SUMMARY

A 52-year-old white diabetic male with 4-weeks history of persistent cough followed by headache, drenching night sweats, low-grade fever, worsening photophobia, nausea and vomiting was presented. Examination was significant for photophobia and diminution of vision. His spinal fluid and blood cultures were positive for *Cryptococcus neoformans*. Intravenous fluconazole were given for 2 weeks followed by oral fluconazole. There was significant improvement in systemic and ocular symptoms. HIV serology was negative, but his CD4 counts were low with inverted CD4:CD8 ratio.

BACKGROUND

Idiopathic CD4 lymphocytopenia (ICL) was defined by the US Centre for Disease Control and Prevention as a clinical condition in patients with depressed numbers of circulating CD4 T lymphocytes (<300 cells/ μ L or $<20\%$ of total T cells) on more than one occasion at least 6 weeks apart, with no laboratory evidence of infection with HIV-1 or HIV-2 and the absence of any defined immunodeficiency or therapy associated with depressed levels of CD4 T cells.¹ Different case reports of ICL associated with different opportunistic diseases and clinical conditions, mostly fungal, parasitic and viral infections have been published.^{2,3} We report a case of disseminated cryptococcosis presenting as cryptococcal meningitis and chorioretinitis in a clinically unsuspected ICL.

CASE PRESENTATION

A 52-year-old white male was presented with history of persistent cough followed by frontal headache, drenching night sweats, low-grade fever, worsening photophobia, nausea and vomiting for

4 weeks. He consulted his primary care physician and was treated with amoxicillin, ceftriaxone and steroids for possible sinusitis. But there was no improvement and was brought into emergency room because of severe headache and weakness with diminution of vision of left eye. At the time of presentation, he had persistent headache and photophobia. He had no risk factors for HIV infection and had not received any immunosuppressive drugs. His medical history was significant for diabetes mellitus. He worked as a musician and denied smoking or alcohol intake. He had no pets and no recent travel. Family history was unremarkable. Physical examination was within normal limits except for photophobia and reduce left eye vision described as a scotoma. In addition, ophthalmology was consulted and revealed visual acuity OD 20/20, OS 20/50, normal anterior segment except bilateral nuclear sclerosis grade 1 changes. Left eye also revealed an inner retinal 1DD white creamy spot superotemporal to fovea which was further confirmed on an optical coherence tomography as a subretinal deposit. It was presumed to be a focal cryptococcal chorioretinitis involving the left eye after further workup (figures 1 and 2).

INVESTIGATIONS

Laboratory tests revealed a leucocyte count of 12.5×10^9 /L (neutrophils 83%). He had normal renal and liver function panel. A lumbar puncture revealed an opening pressure of 18 mm H₂O, leucocyte count of 28×10^6 /L (neutrophils 30%, lymphocytes 25%, monocytes 34%) with no erythrocytes, glucose of 92 mg/dL (corresponding blood glucose of 194 mg/dL) and proteins 47 mg. Cerebrospinal fluid (CSF) gram stain, fungal and acid-fast bacilli stain was negative. CSF and blood cryptococcal antigen were positive with significant titres (1:10 and 1:80, respectively). Blood culture and CSF fungal culture grew *Cryptococcus neoformans* which confirmed the diagnosis of cryptococcal meningitis and disseminated cryptococcosis. CT chest showed a 7 mm left upper nodule.

TREATMENT

Treatment with liposomal amphotericin (5 mg/kg) was started, but patient developed acute renal failure within 48 hours and was switched to intravenous fluconazole 800 mg loading dose followed by 400 mg daily.

Intravenous antifungals were continued for 2 weeks followed by oral fluconazole for 8 weeks (400 mg daily) and maintained on prophylactic dose of 200 mg daily. There was significant improvement in systemic and ocular symptoms.

Figure 1 Fundus picture of left eye depicting an inner retinal 1DD white creamy spot superotemporal to fovea.

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Figure 2 Montage view of the left eye confirming an inner retinal white creamy spot superotemporal to fovea with clear periphery.

Patient's HIV serology was negative but CD4 counts were low (12/ μ L); CD8 counts were normal (176/ μ L) and an inverted CD4:CD8 ratio (0.1). Immunoglobulin (Ig) levels were within normal (IgG 893 mg/dL, IgM 92 mg/dL, IgA 156 mg/dL).

OUTCOME AND FOLLOW-UP

After 1 year of follow-up, the patient continued to have a depleted CD4+ cell count (2/ μ L). Serial serum cryptococcal antigen measurements continued to improve (1:64). The results of a repeat HIV test were negative. Repeat lumbar puncture revealed clear CSF with leucocyte count $<1 \times 10^6$ /L and 25 mg protein, and CSF cryptococcal antigen and fungal culture were negative after initiation of treatment. The patient was otherwise well and maintained on prophylactic therapy with fluconazole 200 mg orally.

DISCUSSION

ICL in an immunocompetent adult is rarely seen, unlike transient CD4 lymphocytopenia, which is common and occur in 0.4%–4.1% healthy HIV-negative individuals at any given time.² It is a heterogeneous condition diagnosed typically in middle age, usually after an opportunistic infection.² ICL is a diagnosis of exclusion and requires an extensive immunological, hematological, rheumatological and infectious disease workup and requires a follow-up testing to confirm the persistence of lymphocytopenia.

Various opportunistic bacterial, viral, parasitic and fungal diseases may depress CD4 cell counts, but preserved the CD4:CD8 ratio.⁴ The most important differential diagnosis of CD4 lymphocytopenia is HIV infection. ICL has constantly low CD4 counts but with HIV infection there is a progressive drop in CD4 counts.

The opportunistic infections in ICL are similar to those HIV-positive patients with similar CD4 T cell counts. Ahmad *et al*⁵ reviewed 258 cases of ICL. Only 12.4% had no opportunistic infection. The most common organism isolated was *C. neoformans* (69 cases) causing meningitis followed by pneumonia and osteomyelitis. In another study, at presentation, cryptococcal, genital human papilloma virus and non-tuberculous mycobacterial infections were the most common infections.⁶ To the best of our knowledge, there has been no case report of disseminated cryptococcosis with chorioretinitis in ICL.

ICL should always be evaluated for the presence or absence of CD8 T lymphocytopenia. This observation precludes the use of the CD4/CD8 ratio for diagnostic purposes in ICL and supports that it is a syndrome that could be further accompanied by B cell lymphocytopenia.⁷

The disseminated cryptococcosis, cryptococcal meningitis and chorioretinitis in our case was secondary to CD4 lymphocytopenia and it improved following antifungal therapy. Because of the sustained CD4 T lymphocyte depletion, the absence of serological evidence of HIV infection and the absence of any immunosuppressive condition/therapy associated with T cell depletion, our patient met the existing criteria for ICL.

It has been observed by Zonios *et al*⁷ that the CD4 T cell counts in 20% of their patients resolved their lymphocytopenia within 3 years of diagnosis in comparison to the rest of the patients whose CD4 counts remained $<300/\text{mm}^3$ without progression over several years. Therefore, it was thought that it is reasonable to strictly follow-up these patients for the first 3 years because of the risk of serious infections and the possible normalisation of CD4 T cell counts, allowing discontinuation of any prophylaxis.

There is insufficient evidence to guide primary infection prophylaxis but secondary prophylaxis has been recommended. These secondary prophylaxis stemmed from experience in HIV-infected patients. Strategies to increase the circulating CD4 lymphocytes in selected patients with a history of life-threatening infections or profound immunodeficiency could be considered. Therapeutic options used to increase CD4 cells or improve immune function in ICL include the use of IL-2, interferon- γ therapy and IL-7.^{8–10} Complete restoration of CD4 counts to normal levels has been tried with allogeneic bone marrow transplantation.^{11 12}

To define disseminated cryptococcosis, we need at least one positive blood culture or two different site-positive culture.⁶ In our case, we had positive blood and spinal fluid cultures.¹³ In addition, cryptococcal polysaccharide antigen can be helpful in diagnosing cryptococcal infection from both serum and CSF with sensitivity and specificity 100% and 96%–99.5%, respectively, in serum as well as 96%–100% and 93.5%–99.8% in CSF.^{14 15} The recommended treatment in non-HIV infected patients is amphotericin B with or without initial flucytosine for 4 weeks for induction, followed by maintenance treatment with fluconazole at 400–800 mg/day for 8 weeks and reducing the dose to 200 mg/day as suppressive therapy. Currently, there are no well-defined guideline for stopping treatment. In general, treatment can be discontinued when symptoms improve and have at least two negative CSF cultures with normal glucose level. Most patients will remain on fluconazole suppressive therapy for at least 6–12 months to prevent relapse, as there are higher relapse rate in the first year once therapy is discontinued.¹⁶ Due to delay in diagnosis in non-HIV and non-transplant, recipient patients have the worst prognosis.¹⁷ It is imperative to identify patients with high risk for relapse or failure to assess the need for prolonged antifungal regimen.

In summary, we present a non-HIV, non-transplant, in a clinically unsuspected ICL with disseminated cryptococcal disease involving eyes and brain, with positive blood cultures. He was initially treated with amphotericin for induction therapy but switched to fluconazole due to inability to tolerate, with a transition to fluconazole maintenance therapy, which the patient currently remains on. Disseminated cryptococcal infection is a potential cause of serious morbidity and mortality. It can affect both immunocompromised and immunocompetent people. Delayed diagnosis in unusual hosts, such as the non-HIV and non-transplant population, may lead to unfavourable outcomes.

Learning points

- ▶ Consider idiopathic CD4 lymphocytopenia in patients having opportunistic infections with no risk factors for HIV/ immunosuppression.
- ▶ Treatment and prophylaxis of opportunistic infections falls in line with the patients having HIV infection.
- ▶ Routine follow-up of such patients is recommended.

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REFERENCES

- 1 Centers for Disease Control (CDC). Unexplained CD4+ T-lymphocyte depletion in persons without evident HIV infection--United States. *MMWR Morb Mortal Wkly Rep* 1992;41:541–5.
- 2 DeHovitz JA, Feldman J, Landesman S. Idiopathic CD4+ T-lymphocytopenia. *N Engl J Med* 1993;329:1045–6.
- 3 Smith DK, Neal JJ, Holmberg SD. Unexplained opportunistic infections and CD4+ T-lymphocytopenia without HIV infection. An investigation of cases in the United States. The Centers for Disease Control Idiopathic CD4+ T-lymphocytopenia Task Force. *N Engl J Med* 1993;328:373–9.
- 4 Sharma A, Lal V, Modi M, et al. Idiopathic CD4 lymphocytopenia presenting as refractory cryptococcal meningitis. *Ann Indian Acad Neurol* 2010;13:136–8.
- 5 Ahmad DS, Esmadi M, Steinmann WC. Idiopathic CD4 Lymphocytopenia: spectrum of opportunistic infections, malignancies, and autoimmune diseases. *Avicenna J Med* 2013;3:37–47.
- 6 Zonios D, Sheikh V, Sereti I. Idiopathic CD4 lymphocytopenia: a case of missing, wandering or ineffective T cells. *Arthritis Res Ther* 2012;14:222.
- 7 Zonios DI, Falloon J, Bennett JE, et al. Idiopathic CD4+ lymphocytopenia: natural history and prognostic factors. *Blood* 2008;112:287–94.
- 8 Sternfeld T, Nigg A, Belohradsky BH, et al. Treatment of relapsing *Mycobacterium avium* infection with interferon-gamma and interleukin-2 in an HIV-negative patient with low CD4 syndrome. *Int J Infect Dis* 2010;14(Suppl 3):e198–201.
- 9 Holland SM, Eisenstein EM, Kuhns DB, et al. Treatment of refractory disseminated nontuberculous mycobacterial infection with interferon gamma. A preliminary report. *N Engl J Med* 1994;330:1348–55.
- 10 US National Library of Medicine. Interleukin-7 (CYT107) Treatment of Idiopathic CD4 Lymphocytopenia: Expansion of CD4 T Cells (ICICLE). 2015.
- 11 Petersen EJ, Rozenberg-Arska M, Dekker AW, et al. Allogeneic bone marrow transplantation can restore CD4+ T-lymphocyte count and immune function in idiopathic CD4+ T-lymphocytopenia. *Bone Marrow Transplant* 1996;18:813–5.
- 12 Cervera C, Fernández-Avilés F, de la Calle-Martin O, et al. Non-myeloablative hematopoietic stem cell transplantation in the treatment of severe idiopathic CD4+ lymphocytopenia. *Eur J Haematol* 2011;87:87–91.
- 13 Yehia B, Eberlein M, Sisson SD, et al. Disseminated cryptococcosis with meningitis, peritonitis, and cryptococcemia in a HIV-negative patient with cirrhosis: a case report. *Cases J* 2009;2:170.
- 14 Kauffman CA, Bergman AG, Severance PJ, et al. Detection of cryptococcal antigen. Comparison of two latex agglutination tests. *Am J Clin Pathol* 1981;75:106–9.
- 15 Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. *Clin Infect Dis* 2010;50:291–322.
- 16 Perfect JR. Cryptococcosis (*Cryptococcus neoformans* and *Cryptococcus gattii*). In: Bennett JE, Dolin R, Blaser MJ, eds. *Principles and practice of infectious diseases*. Philadelphia, PA, USA: Elsevier Saunders, 2015:2934–48.
- 17 Bratton EW, El Hussein N, Chastain CA, et al. Comparison and temporal trends of three groups with cryptococcosis: HIV-infected, solid organ transplant, and HIV-negative/non-transplant. *PLoS One* 2012;7:e43582.

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