Abstract

A 39 years old HIV-positive black African woman with previously treated cerebral toxoplasmosis experienced a foetal intra-uterine death due to congenital toxoplasmosis. This case demonstrates the complexities of screening for maternal toxoplasmosis in the context of pregnancy and HIV-infection related cell-mediated immunosuppression. Additionally, the case highlights the challenges in providing effective preventative and therapeutic drug options for congenital toxoplasmosis.

Case Presentation

A 39 years old black African woman presented with four weeks of worsening headache, slurred speech and left-sided weakness. Cranial MRI showed multiple ring-enhancing lesions with mass effect, thus lumbar puncture was contraindicated. An HIV-1 antibody test was positive: CD4 count was 67 (7%) cells/mm^3 and HIV viral load (VL) was 188,895 copies/ml. Given the advanced immunosuppression, the clinical and radiological features, cerebral toxoplasmosis was diagnosed. Sulphadiazine 2g QDS, and pyrimethamine 75mg OD, with calcium folinate 15mg OD were commenced. Subsequently toxoplasma serology was IgG positive and IgM negative. Plasma PCR for *Toxoplasma* DNA was not done. Ten days into treatment acute kidney injury (AKI) developed, and sulphadiazine was switched to clindamycin 600mg QDS. After six weeks of treatment there was an appropriate clinical and radiological response, and secondary prophylaxis (dapsone 100mg OD and weekly pyrimethamine 50mg with calcium folinate 15mg OD) was started. Antiretroviral therapy (abacavir/lamvivudine and efavirenz) was started three weeks after starting toxoplasmosis treatment. After four months the VL was undetectable and CD4=199 (12%)

cells/mm^3. After thirteen months of ART she presented with her third pregnancy at 12/40 gestation (VL undetectable, CD4=296 (18%) cells/mm^3). Toxoplasma prophylaxis was discontinued, as per UK guidelines: CD4 >200 cells/mm^3 and VL undetectable for >6 months, and risk of teratogenicity from the medication[1].

At 32^{+6}/40 gestation she reported fever for a week. Clinical examination and foetal monitoring were normal. Elevated ALT=69 IU/L (previously <20) and C-reactive protein (CRP) =84 mg/L were noted (CD4=333 (13%) cells/mm^3, VL undetectable). A week later the fever persisted with a further rise in ALT=298 IU/L and CRP=91 mg/L. A septic screen, chest and abdominal imaging did not yield a diagnosis. At 34^{+5}/40 she suffered a foetal death in-utero (FDIU) (at this time CD4=271 (11%) cells/mm^3, VL was undetectable). A macerated foetus of appropriate gestational development was delivered. The fever, ALT and CRP normalised post-delivery.

Foetal necropsy results, available 12 weeks post-FDIU, demonstrated *T. gondii* tachyzoites within the foetus and placenta. Maternal plasma samples were retrospectively tested; samples from four days before the FDIU were Toxoplasma DNA, dye test (4000 IU/mL), and immunosorbent agglutination assay IgM positive. Additionally, maternal plasma samples obtained two months and 1 year previously were negative for Toxoplasma DNA.

The patient was advised against conceiving again pending advice from a multidisciplinary team (MDT: HIV infectious diseases obstetrics, and neonatology). Fourteen weeks after the FDIU she again became pregnant. The MDT's consensus was to re-treat for reactivation of toxoplasmosis, although the timing of this with a new pregnancy was unclear. The risks of teratogenic medications in the first trimester outweighed any benefit

of re-treating. The patient elected to take azithromycin 1g three times/week prophylactically (with pyrimethamine from the second trimester). Re-screening for active toxoplasmosis (maternal plasma DNA and IgM) was negative. She miscarried at 12/40 gestation (CD4=374 (19%) cells/mm^3, VL undetectable); foetal necropsy excluded toxoplasmosis and maternal plasma Toxoplasma DNA and IgM remained negative.

Despite no evidence of active toxoplasmosis (undetectable toxoplasma DNA, normal cranial MRI and ophthalmology review), latent uterine infection could not be excluded. Re-treatment was commenced using sulphadiazine, pyrimethamine, and calcium folinate (doses as above). Due to severe nausea and vomiting, AKI and transaminitis, sulphadiazine was switched to azithromycin 500mg BD with pyrimethamine OD. After five weeks secondary prophylaxis was commenced using weekly azithromycin 1g, and daily pyrimethamine 25mg and calcium folinate. After a year of follow up the patient remains well.

Discussion

This is a case of congenital toxoplasmosis causing an FDIU in a patient with stable HIV and previously treated cerebral toxoplasmosis. Congenital toxoplasmosis occurs from primary seroconversion during pregnancy or reactivation of latent uterine infection as a result of pregnancy-associated cell-mediated immunosuppression and HIV co-infection[2].The incidence of congenital toxoplasmosis in HIV coinfection is low (0.72%) and cases have been reported in normal CD4 counts[2–4].

The British HIV Association recommends antenatal toxoplasma serology testing with foetal screening if there is evidence of active/reactivation of maternal infection, and

primary prophylaxis is given if CD4 <200 cells/mm^3 [1]. Our patient had demonstrated an appropriate clinical and radiological response to toxoplasma therapy and so this had been discontinued accordingly. Neither repeat toxoplasma serology nor plasma DNA PCR were tested before discontinuing secondary prophylaxis and this is not indicated in current guidelines. In non-pregnant HIV+ individuals the rate of reactivation toxoplasmosis following discontinuation of secondary prophylaxis (once CD4 >200) has been reported as low as 4.5%[5].

The prescribed maintenance therapy deviated from guidelines as dapsone 100mg OD with pyrimethamine 50mg weekly was given instead of pyrimethmine 25mg OD. This raises the possibility that the congenital transmission of toxoplasma occurred from reactivation from partially treated or latent infection. The uterus and placenta can act as reservoirs supplying viable organisms to the foetus throughout pregnancy and perinatal transmission is reported to be more common in the later stages of pregnancy[6,7]. Congenital toxoplasmosis can cause in-utero growth retardation. In this case the foetus was of appropriate gestational development at the time of FDIU, which suggests transmission may have occurred in late pregnancy. Late trimester congenital infection has also been reported in HIV infected individuals[2].

Antenatal screening is challenging as toxoplasma antibodies can be falsely negative in immunodeficient patients and IgM antibodies can persist for up to 18 months following infection[8]. Maternal toxoplasma DNA PCR testing, ultrasonographic foetal monitoring and amniocentesis to identify *T. gondii* DNA are possible screening and diagnostic options but are not recommended in routine practice in the UK. An amniocentesis was not performed prior to the FDIU in our patient as there were no obstetric or clinical

indications. Amniocentesis is recommended after 18/40 gestation (to reduce false negative results) and this would have been a potential option had our patient not miscarried her subsequent pregnancy at 12/40 gestation[9].

Current treatment and prevention options in adults (pyrimethamine, sulphadiazine, trimethoprim-sulphamethoxazole and azithromycin) are contraindicated in pregnancy due either to teratogenicity in the first trimester, foetal bone marrow suppression or foetal and maternal cardiac arrhythmia. Additionally, these drugs do not prevent transmission or treat active congenital toxoplasmosis. Spiramycin does not readily cross the placenta and so can only be used as prophylaxis in pregnancy before congenital transmission occurs as it is ineffective for treating congenital toxoplasmosis[4]. Dapsone crosses the placenta and has been used safely as prophylaxis for leprosy and malaria in pregnancy however, there is a risk of maternal and foetal haemolytic anaemia in the context of G6PD deficiency[10–12].

Congenital toxoplasmosis in HIV-exposed infants is rare even in pregnancy-related cell-mediated immunosuppression. Routine maternal toxoplasma DNA monitoring along with ultrasonographic foetal monitoring throughout pregnancy in co-infected mothers may be a useful screening tool with amniocentesis if clinically indicated. It is unclear whether continuation of prophylaxis would have prevented reactivation in this case. Improved screening techniques, prevention and treatment options for congenital toxoplasmosis in HIV-infected women are needed.

References

1. Nelson M, Dockrell D, Edwards S. British HIV Association and British Infection Association guidelines for the treatment of opportunistic infection in HIV-seropositive individuals 2011. *HIV Med*. 2011;12(s2):1-5. doi:10.1111/j.1468-1293.2011.00944_1.x.

2. Campos FA, Queiroz De Andrade GM, De A, et al. Incidence of congenital toxoplasmosis among infants born to HIV-coinfected mothers: case series and literature review. 2014;1(86):609-617. doi:10.1016/j.bjid.2014.05.008.

3. Biedermann K, Flepp M, Fierz W, Joller-Jemelka H, Kleihues P. Pregnancy, immunosuppression and reactivation of latent toxoplasmosis. *J Perinat Med*. 1995;23(3):191-203. http://www.ncbi.nlm.nih.gov/pubmed/8568611. Accessed June 25, 2017.

4. Montoya JG, Remington JS, Remington JS. Clinical Practice: Management of *Toxoplasma gondii* Infection during Pregnancy. *Clin Infect Dis*. 2008;47(4):554-566. doi:10.1086/590149.

5. Bertschy S, Opravil M, Cavassini M, et al. Discontinuation of maintenance therapy against toxoplasma encephalitis in AIDS patients with sustained response to anti-retroviral therapy. *Clin Microbiol Infect*. 2006;12(7):666-671. doi:10.1111/j.1469-0691.2006.01459.x.

6. Dubey JP, Jones JL. Toxoplasma gondii infection in humans and animals in the United States. *Int J Parasitol*. 2008;38(11):1257-1278. doi:10.1016/j.ijpara.2008.03.007.

7. Garweg JG, Scherrer J, Wallon M, Kodjikian L, Peyron F. Reactivation of ocular toxoplasmosis during pregnancy. *BJOG An Int J Obstet Gynaecol*. 2005;112(2):241-242. doi:10.1111/j.1471-0528.2004.00302.x.

8. Tekkesin N. Diagnosis of toxoplasmosis in pregnancy: a review. *HOAJ Biol*. 2012;1(1). doi:10.7243/2050-0874-1-.

9. Romand S, Wallon M, Franck J, Thulliez P, Peyron F, Dumon H. Prenatal diagnosis using polymerase chain reaction on amniotic fluid for congenital toxoplasmosis. *Obstet Gynecol*. 2001;97(2):296-300. http://www.ncbi.nlm.nih.gov/pubmed/11165598. Accessed February 11, 2018.

10. Zuidema J, Hilbers-Modderman ESM, Merkus FWHM. Clinical Pharmacokinetics of Dapsone. *Clin Pharmacokinet*. 1986;11(4):299-315. doi:10.2165/00003088-198611040-00003.

11. Newman RD, Parise ME, Slutsker L, Nahlen B, Steketee RW. Safety, efficacy and determinants of effectiveness of antimalarial drugs during pregnancy: implications for prevention programmes in Plasmodium falciparum-endemic sub-Saharan Africa. *Trop Med Int Heal*. 2003;8(6):488-506. doi:10.1046/j.1365-3156.2003.01066.x.

12. Thornton YS, Bowe ET. Neonatal hyperbilirubinemia after treatment of maternal leprosy. *South Med J*. 1989;82(5):668. http://www.ncbi.nlm.nih.gov/pubmed/2717998. Accessed February 11, 2018.