

I

## Symptomatic Primary Cytomegalovirus Infection in an HIV Positive Pregnant Woman.

Bergin S, Ferguson W, Corcoran S, Varughese A, Byrne D, Lawless M, Eogan M, Lambert JS.

### Summary:

We describe a case of symptomatic primary Cytomegalovirus (CMV) infection in an HIV positive pregnant woman on anti-retroviral (ARV) treatment with a CD4 count  $>200 \times 10^6/l$  requiring intravenous (IV) ganciclovir. No adverse consequences from ganciclovir or evidence of congenital CMV infection were found.

### Short introduction stating the reasons for reporting the case:

Pregnancy related immunosuppression predisposes women to infection. Symptomatic primary CMV infection is rare in pregnancy but should be considered in pregnant women presenting with “viral” symptoms particularly those immunocompromised.

### Case report including history, investigations and treatment:

A 21-year-old pregnant woman with a three year history of HIV-1 developed pyrexia, cough, chest pain and epigastric pain at 30 weeks gestation. She was treatment naïve without evidence of HIV resistance. At first antenatal visit (13 weeks gestation), CD4 count was  $862 \times 10^6/l$  (53%). HIV viral load (VL) was 4,645copies/ml. Atazanavir, ritonavir and zidovudine/lamivudine were commenced at 17 weeks gestation.

On examination, the patient was pyrexial ( $38.7^\circ\text{C}$ ), tachypnoeic (respiratory rate 20/min) with bilateral crepitations and tachycardic (pulse 123 beats/min). Oxygen saturations were 98% in room air. Investigations revealed a

Formatted: Font color: Auto

Formatted: Line spacing: 1.5 lines

leukocytosis of  $15.2 \times 10^9/l$ , neutrophils  $13.9 \times 10^9/l$ ; C-reactive protein (CRP) 29 mg/l and elevated liver enzymes. Chest x-ray showed minor linear shadowing at the right lung base. She was diagnosed with a respiratory tract infection and commenced on broad-spectrum antimicrobial therapy, but remained febrile.

Serology revealed CMV IgM and CMV IgG positivity with an IgG avidity index of 0.174, indicating recent infection. CMV DNA viral load was 97,129 copies/ml(cpm), Retrospectively tested booking antenatal serology was CMV negative. Other viral studies were negative confirming symptomatic primary CMV infection. Of note, at 18 weeks gestation the patient was admitted with a diffuse, maculo-papular, erythematous rash with low-grade pyrexia attributed to recent initiation of ARV therapy. However, this likely represented CMV seroconversion.

Following careful consideration 300mg ganciclovir (5mg/kg) IV 12 hourly was commenced. The patient became afebrile, liver enzymes, WCC and CRP normalized. IV treatment continued for 7 days, followed by oral valgancyclovir 900mg twice daily until delivery. Zidovudine/lamivudine was changed to tenofovir/emtricitabine to avoid interaction with valgancyclovir. CMV DNA was undetectable four weeks after ganciclovir initiation

Serial fetal ultrasounds showed reduced fetal growth. Pericardial effusion and right ventricular hypertrophy were initially noted but spontaneously resolved prior to delivery. Labour was induced at 37 weeks gestation. The female infant was small for gestational age (2.07kg) but otherwise clinically unremarkable. Neonatal FBC and liver enzymes were normal. Congenital CMV infection was out-ruled with infant urine and plasma CMV DNA undetectable at 3, 14 and 42 days of life. Infant HIV status was negative.

### Discussion referring to relevant literature

Congenital CMV affects 0.3-2.4% of all live births in developed countries<sup>1</sup>. Seroconversion occurs in 1-4% of all pregnancies and is higher in women who are of low socioeconomic status<sup>2</sup>. Primary CMV infection during pregnancy carries a high risk (30-40%) of congenital infection; the risk of congenital infection associated with CMV reactivation is much lower (0.5-1.4%)<sup>3</sup>, but the consequences to the infant are equally severe<sup>4</sup>. Infection in early pregnancy carries a higher risk of an affected fetus than later infection<sup>5</sup>. Complications include intrauterine death, sensorineural hearing loss (SNHL) and neurodevelopmental delay<sup>5</sup>. While only 10-20% of affected newborns have symptomatic infection, 5-15% develop late sequelae during the first years of life, namely SNHL<sup>3,5</sup>.

CMV seroprevalence among women of childbearing age varies from 35%-95% depending on country of origin, socioeconomic status, age, race, breastfeeding practices, sexual activity and use of group childcare facilities<sup>4,6</sup>. CMV transmission occurs via close, non-sexual contact, sexual activity, breast-feeding, blood transfusions, organ transplantation and contact with the urine and saliva of young children<sup>7</sup>. CMV seroprevalence among Irish pregnant women is 30.4%, leaving most at risk of primary infection<sup>4</sup>.

The patient's CD4 count was  $700 \times 10^6/l$ , and HIV viral load  $<40$  at the estimated time of CMV seroconversion. Pregnancy-associated depression of cell-mediated immunity (CMI) may interfere with the response to specific infectious agents<sup>8</sup>. One study showed specific impairment in CMI to CMV in mothers of infants with congenital CMV infection<sup>9</sup>. In another, CMV seropositive parturients had markedly depressed lymphocyte proliferative responses, suggesting reactivation of latent CMV related to transient depression of CMV-specific cellular immunity<sup>10</sup>. We postulate that pregnancy-related CMI suppression contributed to symptomatic CMV infection in a patient with existing immune dysfunction.

Ganciclovir is not licensed in pregnancy, as animal studies have demonstrated teratogenicity, however, a number of published case reports describe the safe use of ganciclovir during pregnancy without adverse fetal outcome<sup>11,12</sup>. Our HIV infected patient had a high CMV viral load (97,129cpm) and was clinically symptomatic, hence the decision to treat for both maternal and fetal benefit. The patient was beyond trimester one when drug toxicity to the fetus is greatest. Both IV and oral anti CMV antivirals were administered until delivery without adverse fetal outcome.

This report describes a rare case of primary CMV infection in a HIV-infected woman on ARVs in pregnancy. CMV-specific antiviral therapy was safely administered with a good outcome for both mother and child.

#### References:

- (1) Bonalumi S, Trapanese A, Santamaria A, D'Emilio L & Mobii L. Cytomegalovirus infection in pregnancy: review of the literature. *J. Prenat Med* 2011 Jan-Mar; 5 (1):1-8
- (2) SOGC Clinical Practice Guideline. Cytomegalovirus infection in pregnancy. No 240 April 2010
- (3) Lopo S, Vinagre E, Palminha P, Paixo MT & Freitas MG. Seroprevalence to cytomegalovirus in the Portuguese population, 2002 – 2003 *Euro Surveill.* 2011; 16(25)
- (4) Knowles SJ, Grundy K, Cahill I, Cafferky MT & Geary M. Low cytomegalovirus sero- prevalence in Irish pregnant women. *Ir Med J.* 2005 Jul-Aug; 98(7)210-2
- (5) Bhide A and Papageorgiou A. Managing primary CMV infection in pregnancy. *BJOG* 2008; 115: 805-807
- (6) De Paschale M, Agrappi C, Manco MT, Paganini A & Cleria P. Incidence and risk of cytomegalovirus infection during pregnancy in an urban area of Northern Italy. *Infect Dis Obstet Gynecol.* Vol 2009; Article ID 206505 5 pages.

- (7) Colugnati F, Staras S, Dollard S & Cannon MJ. Incidence of cytomegalovirus infection among the general population and pregnant women in the United States. *BMC Infect Dis.* 2007;7:71
- (8) Weinburg E D. Pregnancy – associated depression of cell- mediated immunity. *Rev Infect Dis* 1984 Nov – Dec ;6 (6): 814-831
- (9) Rola – Plezczynski M, Frenkel LD, Fuccillo D, Henson SA, Vincent MM, Reynolds DW, Stagnos S & Bellanti JA. Specific impairment of cell mediated immunity in mothers of Infants with congenital infection due to cytomegalovirus. *J Infect Dis* (1977) Mar 135 (3):386-391
- (10) Gherz RC, Christianson WR, Liner KM, Conroy MM, McCabe SA & Balfour HH Jr. Cytomegalovirus – specific humoral and cellular immune responses in human pregnancy. *J Infect Dis* (1981) Mar 143 (3); 391-395
- (11) Puliyanda DP, Silverman NS, Lehman D, Vo A, Bunnapradist S, Radha RK, Toyoda M & Jordan SC. Successful use of oral ganciclovir for the treatment of intrauterine cytomegalovirus infection in a renal allograft recipient. *Transpl Infect Dis* 2005 Jun 7 (2) 71-74
- (12) Pescovitz MD. Absence of teratogenicity of oral ganciclovir used during early pregnancy in a liver transplant recipient. *Transplantation.* 1999 Mar 15; 67(5):758-9.