Unusual association of diseases/symptoms

Cytomegalovirus infection in association with early onset pre-eclampsia

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Summary

This case describes a woman who presented with raised α -fetoprotein (AFP) on second trimester screening, and developed early onset fetal growth restriction (FGR) and severe pre-eclampsia (PET) before 24 weeks' gestation requiring magnesium sulphate and intravenous antihypertensives. Ultrasonography revealed a structurally normal fetus with estimated weight <3rd centile, abnormal uterine artery Dopplers and deteriorating fetal arterial Dopplers over the following 2 weeks. The pregnancy ended in fetal death before a viable weight was reached. Postmortem examination revealed a growth restricted fetus (birth weight <0.4th centile) and chronic villitis secondary to placental cytomegalovirus (CMV) infection. CMV has previously been associated with PET and FGR. This case highlights its potential role in the pathogenesis of placental failure and has relevance for counselling and management for future pregnancies. Furthermore, raised AFP may represent ongoing placental damage and offers potential for future therapeutic measures—for example, antivirals or immunisations to alter the natural history and prognosis of placental infection.

BACKGROUND

Pre-eclampsia (PET) is a condition specific to pregnancy and the puerperium: defined as hypertension >140/90 mm Hg and proteinuria >300 mg/24 h occurring after 20 weeks' gestation and resolving after conclusion of pregnancy. It affects 2–3% of pregnancies in the UK, with certain groups being at higher risk than others, and accounts for a significant proportion of maternal and neonatal morbidity and mortality worldwide. In addition, there are increasingly recognised associations between a history of PET and the development of cardiovascular disease in later life.^{1–8} The pathogenesis of PET remains unclear but it is increasingly apparent that early onset and late onset PET are differing pathologies; early onset PET has a particularly poor maternal and fetal prognosis.⁹

A role for infection in the pathogenesis of PET has been proposed and the evidence supporting this theory is growing. One infection that has been implicated in the aetiology of PET is cytomegalovirus (CMV), which is a common infection in pregnant women (1–4% of pregnancies).¹⁰ This case highlights the possible role of CMV in disorders of abnormal placental development, and raises the potential for development of future prophylactic and therapeutic agents. In addition, knowledge of a CMV infection will impact significantly on postnatal counselling and the management of subsequent pregnancies.

CASE PRESENTATION

A 32-year-old, ex-smoker, who worked as a restaurant manager presented for antenatal care at 7 weeks' gestation (calculated from ultrasonographic parameters). At booking, her body mass index was 31.7, blood pressure was 125/82 mm Hg and dipstick urinalysis was negative for proteinuria. This was her second pregnancy; the first had

resulted in first trimester spontaneous abortion at 6 weeks' gestation 3 years previously. Her only significant medical history was of transient hypertension induced by the combined oral contraceptive pill.

Blood was collected to screen for neural tube defects and fetal aneuploidies at 17⁺2 weeks' gestation, which demonstrated increased α -fetoprotein (AFP; 4.66 multiples of the median (MoM)) and human chorionic gonadotrophin (HCG; 4.21 MoM) levels. The calculated individual risk of Down's syndrome was 1:65. Minor vaginal bleeding had occurred at 6 weeks' gestation and there was no history of maternal illness or infection during the pregnancy. At this stage, amniocentesis for fetal karyotyping was declined. Detailed ultrasonography at 18 weeks demonstrated no fetal structural defects but severe fetal growth restriction (FGR) with estimated fetal weight below the 3rd centile. No Doppler studies were performed at this stage and no viral screen was conducted. In view of severe early onset FGR, the patient was counselled regarding the poor prognosis, the risk of aneuploidy (5–10%) and the risk of a genetic syndrome as the underlying pathology. Amniocentesis and termination of pregnancy was offered and the patient chose expectant management without invasive testing. Thus, serial ultrasonographic assessments were planned (see below). She was screened for inherited and acquired thrombophilias as these have been associated with severe FGR. While there is no evidence that any subsequent anticoagulant treatment would have improved the outcome in this pregnancy, this knowledge may have modified maternal risks for venous thromboembolism and informed the management of future pregnancies.

The patient was referred for blood pressure monitoring at 22 weeks' gestation due to borderline hypertension with systolic blood pressure 130–140 mm Hg and diastolic blood pressure 80–90 mm Hg. Transient proteinuria of +

on dipstick testing (in absence of cultured infection) was noted. Low dose aspirin treatment and outpatient blood pressure monitoring was started. At 23⁺⁵ weeks' gestation, asymptomatic severe hypertension of 197/110 mm Hg and proteinuria 4+ (on dipstick test) developed. Severe early onset PET was diagnosed and the patient was admitted from antenatal clinic to delivery unit for investigation and management. There were no unusual or infective symptoms or signs at the time of admission.

INVESTIGATIONS

Serum screening at 17⁺² weeks

AFP 4.66 MoM, human chorionic gonadotropin (HCG), 4.21 MoM and UE3 0.59 MoM.

Ultrasound assessment at 18 weeks

Severe FGR; structurally normal.

Repeat ultrasound assessment at 20 weeks

Severe FGR, fetal size <3rd centile for gestational age and normal amniotic fluid volume.

Immunology, thrombophilia and lupus anticoagulant screen at 20 weeks

Lupus anticoagulant: not demonstrated; antinuclear antibody: negative; immunoglobulin G (IgG) ds-DNA antibody: <25; cardiolipin G: <10; cardiolipin M: <10; antithrombin: 97 (80–110); factor V Leiden mutation: not detected; heterozygous for prothrombin G20210A variant; protein C: 116 (62–126); and free protein S: 58 (44–176).

Uterine artery Doppler assessment (as part of a clinical trial) at 22 weeks

Left: resistance index (RI) 0.99 notched; right: RI 0.9, no notch.

Urinary protein quantification at 23⁺⁵ weeks

2.12 g/24 h.

Key blood results

See table 1.

Table 1 Blood results

	23 ⁺⁵	24 ⁺¹	24 ⁺²	24 ⁺³	24 ⁺⁶	25 ⁺¹	25 ⁺³	Date of delivery	Normal range in pregnancy
Urea	5.1	8.9	9.5	8.0	7.4	6.9	6.2	4.0	2.8–3.8
Creatinine	52	83	70	60	77	81	74	65	50–80
Urate	0.36	0.48	0.41	0.38	0.46	0.45	0.43	0.43	0.14–0.35
Platelets	239	204	194	169	189	175	156	189	100–450

Key ultrasound results

See table 2.

Table 2 Ultrasound results

	23 ⁺⁶	24 ⁺⁴	25 ⁺²
EFW	370g	377g	377g
LV	Normal	Normal	Normal
Umbilical artery EDF	Absent	Absent	Reversed
MCA Doppler	Compensatory	Reduced compensation	Decompensation
DV a Wave	Positive	Absent	Reversed

EFW, estimated fetal weight; LV, liquor volume; EDF, end diastolic flow; MCA, middle cerebral artery; DV, ductus venosus.

Postmortem examination (key findings)

Placenta: 18×12 cm; 137 g (<3rd centile for singleton deliveries); central cord; three vessels; multiple infarcts, abnormal maternal vessels with fibrinoid necrosis and atherosclerosis; focal areas of villous hypoplasia; and at least one focus of chronic villitis—a feature that is entirely in keeping with congenital CMV infection.

Body: 251 g (<0.4th centile for gestation); CMV PCR positive in liver and lung (102 000 000 copies/ml); CMV inclusion bodies identified in lung; and no congenital abnormality/malformation.

Karyotype: 46 XY. Microarray testing: culture failed.

TREATMENT

The patient was managed according to the North West Pre-eclampsia Protocol with direct blood pressure monitoring via an arterial line, fluid restriction to 80 ml/h, strict fluid balance and low molecular weight heparin thromboprophylaxis. Magnesium sulphate treatment was started to prevent the development of eclampsia. Maternal hypertension was unresponsive to both oral and intravenous boluses of labetalol and required an intravenous labetalol infusion (160 mg/h) to maintain systolic blood pressure 130–150 mm Hg and diastolic blood pressure 80–110 mm Hg. Ultrasound assessment at 23⁺⁶ weeks' gestation after maternal stabilisation revealed an active fetus of estimated weight 370 g, with absent end diastolic flow, compensatory middle cerebral artery Doppler waveform and the ductus venosus 'a wave' remained positive. In view of severe maternal illness, termination of pregnancy was offered; however, following discussion between obstetricians, neonatologists, the patient and her partner, an expectant management plan of betamethasone administration, twice daily fetal heart auscultation to confirm viability, alternate day ultrasound and Doppler assessment and consideration of delivery if fetal weight >500 g was achieved or maternal health was further compromised. Use of betamethasone at gestations under 24 weeks is not supported by a robust evidence base; however, in this case it was felt that a single course of betamethasone was unlikely to do harm to mother and

fetus and may have had some effect on fetal lung maturation if a viable weight had been achieved.

Following betamethasone administration (23⁺⁶ to 24⁺⁰ weeks' gestation), regular long acting nifedipine treatment was started and intravenous labetalol requirements decreased with the patient being converted to oral labetalol treatment later that day. Magnesium sulphate infusion was subsequently discontinued at 24⁺¹ weeks' gestation. The couple were counselled that this improvement was likely to have occurred as a response to steroid administration and that clinical parameters were expected to deteriorate again over the coming days. At 24⁺³ weeks' gestation, rebound hypertension occurred requiring increased oral antihypertensive dosage, intravenous labetalol bolus and infusion for a period of 4 h. At that time, deterioration in renal function was noted with plasma urea increasing from 5.1 to 9.5 mmol/l.

At 24⁺⁴ weeks' gestation, the patient was transferred to the antenatal ward on oral antihypertensives (nifedipine LA 40 mg once daily, labetalol 400 mg four times daily) for ongoing expectant management. Over the subsequent 5 days, serial ultrasound examinations demonstrated no significant fetal growth (estimated fetal weight 377 g) with ductus venosus 'a wave' becoming minimal and then absent. The couple were counselled that fetal demise was likely to occur. At 25⁺³ weeks' gestation, absence of fetal movements was reported; ultrasound assessment confirmed fetal death in utero and induction of labour was started.

OUTCOME AND FOLLOW-UP

Postnatally, maternal hypertension improved significantly with reduced oral antihypertensive requirements (labetalol 100 mg twice daily). The patient was discharged home with ongoing blood pressure monitoring.

Postmortem examination of the chromosomally normal, severely growth-restricted male fetus (birth weight 251 g; <0.4th centile for gestation) revealed CMV placentitis and fetal congenital CMV infection without evidence of fetal cerebral calcifications or other defects traditionally associated with congenital CMV infection. Placental histology demonstrated multiple infarcts and abnormal maternal vessels with fibrinoid necrosis and atherosclerosis—appearances in keeping with PET. In view of these findings, booking serum was retrospectively examined and demonstrated seronegativity to CMV; 6 week postnatal serum was collected and demonstrated presence of IgM anti-CMV antibodies and absence of IgG anti-CMV antibodies suggesting that a first episode of CMV infection had occurred between these two sampling episodes. Given that there was evidence of fetal and placental infection with CMV, this CMV infection must have occurred prior to delivery although it cannot be definitively proven that the infection had occurred prior to the diagnosis of FGR. The absence of IgG anti-CMV antibodies more than 6 weeks following primary infection with CMV is an interesting finding and may represent a suboptimal immune response to CMV in this individual.

Six weeks after delivery the patient was physically well with blood pressure controlled on low dose labetalol and absent proteinuria. The couple was informed of the postmortem findings; in retrospect they described a viral-

sounding illness occurring in the late first trimester. They were counselled that her baseline characteristics (raised body mass index, probable undiagnosed chronic hypertension in view of history of oestrogen-induced hypertension and ongoing antihypertensive requirements greater than 6 weeks postnatally, and heterozygous prothrombin gene variant) put her at increased risk of developing PET and that CMV infection of the placenta may have precipitated the disease. As seroconversion to CMV had now occurred, future pregnancies were unlikely to be affected by the same pathology. It was planned that she should seek pre-conceptual counselling before future pregnancies, to start folic acid preconceptually and low dose aspirin treatment at first positive pregnancy test and to consider the potential role for low molecular weight heparin treatment in view of her prothrombin gene variant heterozygosity (while this genotype has been associated with a slightly increased risk of thromboembolic disorders, it has not been demonstrated to lead to an increased risk of PET).

DISCUSSION

The diagnosis of CMV infection in this pregnancy has been made on the basis of fetal tissue PCR positivity for CMV DNA and immunohistochemical findings of CMV inclusion bodies and placental chronic villitis. The finding of antenatal IgM anti-CMV seronegativity and postnatal IgM anti-CMV seropositivity supports this. The lack of IgG anti-CMV response despite a minimum interval of 6 weeks from delivery to postnatal sampling (the interval is likely to have been much longer) has been reported in other cases of CMV infection particularly in the immunocompromised patient.¹¹

Gestational CMV infection has been reported in other pregnancies with raised second trimester AFP and HCG levels, some with^{12–13} and some without¹⁴ classic ultrasonographic features of congenital CMV, which include early onset intrauterine growth restriction (IUGR), oligohydramnios, cerebral calcifications, microcephaly, ventriculomegaly, hepatic calcifications, echogenic bowel, fetal ascites or hydrops, and pleural and pericardial infections. Raised levels of AFP and HCG have been postulated to represent ongoing placental damage or inflammation secondary to CMV infection. Indeed, unexplained raised serum markers have been linked with adverse pregnancy outcomes, including low birth weight, stillbirth and placental abruption.¹⁵ Placental damage or inflammation caused by CMV infection may lead to the development of PET.

We identified only one other case of PET associated with CMV infection in the literature review;¹⁶ however, the fetus and placenta were both hydropic in addition to the presence of maternal peripheral oedema of PET (Mirror syndrome). Other than growth restriction, the fetus in the case we have presented displayed no structural abnormalities. A further case reported the combination of CMV infection, IUGR and abnormal umbilical artery Doppler velocimetry without maternal PET.¹⁷ Interestingly, the pattern of IUGR described in this case (cerebral growth velocity relatively spared in comparison to abdominal growth velocity) suggests the presence of placental insufficiency and histological examination of the placenta revealed CMV placentitis.

Research has previously demonstrated an association between PET and chronic or latent infections, including

urinary tract infection and periodontal disease,¹⁸ CMV,^{19–21} Epstein–Barr virus,²¹ herpes simplex virus type 2,²¹ adeno-associated virus,²² and *Chlamydiae pneumoniae*.¹⁹ These are thought to trigger the development of PET by hyperstimulation of the innate immune system and, thus, amplify the inflammatory environment of pregnancy. The mechanism by which this occurs, the effect on trophoblast development and how these lead to the development of PET are unknown. Many of the traditional risk factors for the development of PET, including young age at conception,²³ nulliparity,²³ new sexual partner²³ and a sexual partner who has previously fathered a pregnancy affected by PET,²⁴ can also be interpreted as risk factors for acquiring infections particularly those spread by close contact.

Further support for the role of CMV in the pathogenesis of PET is drawn from parallels with systemic cardiovascular disease and acute organ transplant rejection. Both these conditions bear striking histological similarities with that of PET,^{25–26} have been linked with CMV infection^{27–29} and demonstrate improved clinical outcomes with antiviral treatment.^{30–31}

Serological evidence of immunity to CMV is present in 60–85% of the general population by adulthood.¹⁹ Unlike most other viral infections, secondary or recurrent CMV infection is able to infect the fetus and placenta; the majority of gestational CMV infections occur in women with previous serological immunity to CMV and are rarely of consequence to the fetus.¹⁰ In contrast, primary infections are associated with a 40% rate of transmission to the fetus.¹⁴ CMV infection of the placenta may persist after clearance of systemic infection, such has been demonstrated in the guinea pig.³¹ In the absence of maternal or fetal features associated with CMV infection, CMV infection at the materno–placental interface may be a contributing factor to the placental damage and shallow trophoblast invasion recognised in PET.

This case supports the proposal that CMV (or other latent infections) may trigger development of PET in genetically and/or environmentally susceptible individuals by infecting the placenta. Our patient displayed minor risk factors for the development of PET at booking (body mass index >30, higher than average blood pressure 125/82 for the first half of pregnancy with a past history of oestrogen-induced hypertension) and was subsequently demonstrated to be heterozygous for the prothrombin gene variant G20210A (in the absence of thrombosis of the placenta), which may have rendered her vulnerable to development of PET subsequent to additional placental insults. CMV infection of the placenta appears in this case to have provided that additional placental insult. If the infective-trigger hypothesis is substantiated, treatment or prophylaxis of infection (eg, CMV) may be able to prevent significant placental damage occurring and, thus, avert the development of PET.

Learning points

- ▶ PET is a common cause of maternal and neonatal morbidity worldwide. Early onset PET is less common and possibly represents a differing pathology from that of late onset PET.
- ▶ CMV and other latent infections have been linked to the pathogenesis of early onset PET and may do so by interfering with placental development and trophoblast invasion.
- ▶ Raised AFP in the absence of structural and chromosomal defects in the fetus is a predictor of poor obstetric outcome; this may represent placental damage, such as that caused by infection. Screening for infections, including CMV, in these circumstances is appropriate and evidence of infection should prompt consideration of all management options for the pregnancy.
- ▶ Information regarding infections may provide valuable information for the management of subsequent pregnancy.

Competing interests None.

Patient consent Not obtained.

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