Cytomegalovirus may mimic the presentation of intrahepatic cholestasis and hemolysis, elevated liver enzymes and low platelets in immunosuppressed pregnant women

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Abstract

Most published cases of cytomegalovirus infection in pregnancy relate to congenital abnormalities in neonates infected in early pregnancy, while the mother remains asymptomatic. We describe a diagnostically challenging case of an immunosuppressed woman with scleroderma who developed deranged liver function tests attributed to intrahepatic cholestasis of pregnancy and haemolysis, elevated liver enzymes and low platelets syndrome but was ultimately found to have disseminated cytomegalovirus. Cytomegalovirus can present in a myriad of ways. Clinicians caring for immunocompromised pregnant women should consider cytomegalovirus as a possible differential diagnosis when reviewing abnormal liver function tests.

Keywords

Pregnancy, cytomegalovirus infection, immunocompromised, scleroderma, HELLP syndrome

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Background

Women with recently diagnosed rapidly progressive diffuse cutaneous scleroderma have an unpredictable disease course and a higher risk of renal crises necessitating treatment with potent immunosuppression. Pregnancy is not recommended for the first four years.¹

Cytomegalovirus (CMV) infection, though common in women of childbearing ages, does not pose a significant risk to immunocompetent women.^{2,3}

Case history

Mrs. T was a 32-year-old gravida 3 para 0 woman with diffuse cutaneous scleroderma and polymyositis diagnosed shortly after her second miscarriage.

Seven months later, she presented at 9+ weeks' gestation for antenatal care. On that review, she had diffuse cutaneous thickening to the level of her elbows, telangiectasias, Raynaud's phenomenon, oesophagitis and proximal myopathy necessitating the use of crutches. Serology showed antinuclear antibody 1:2560, positive ribonucleoprotein and Ro antibodies. Her liver and renal function tests were normal (Table 1). She had a dilated lower oesophagus and mild basal interstitial pulmonary fibrosis seen on computerized tomography (CT) scan of the chest but no evidence of pulmonary hypertension on transthoracic echocardiography.

She was taking azathioprine 150 mg and tapering doses of prednisolone. The risks of developing preeclampsia, preterm labor, renal crisis, infection and gestational diabetes were discussed. Termination of pregnancy was advised with a recommendation to delay another pregnancy for five years post diagnosis, but she declined. At 20 weeks' gestation, she was mobilising independently without aids and had a normal anomaly scan and a normal fetal echocardiogram.

At 25⁺¹ weeks, she presented with intense itching with punched out digital ulcers. Her bile acids and alanine transferase (ALT) were raised (Table 1). Intrahepatic cholestasis of pregnancy (ICP) was the most likely diagnosis after the exclusion of Epstein Barr Virus, Hepatitis C

and B, a negative autoimmune screen for smooth muscle antibody, liver and kidney microsomal antibody, mitochondrial antibody, gastric parietal cell antibody and a normal ultrasound of liver. Ursodeoxycholic acid (UDCA) and flucloxacillin were prescribed with plans to treat her digital ulcers with iloprost, which subsequently healed spontaneously. At 27⁺⁵ weeks, rifampicin was added since her bile acids (105 IU/L) and ALT (71 IU/L) remained raised despite a maximal dose of UDCA 2.5 g/day. At 26⁺⁶ weeks, she presented to the maternity day assessment unit with a 'febrile' illness. After extensive investigations which included normal blood and urine cultures, throat swabs, a normal full blood count and liver function tests (LFTs) that were not significantly worse (Table 1), she was ultimately discharged after being found to be afebrile with no clinical signs of infection.

At 31⁺⁶ weeks, she presented with three weeks of increasing shortness of breath and marked muscle weakness. Her pulse rate was 128/min, blood pressure (BP) was 118/78 mm Hg, respiratory rate was 28/min and oxygen saturation was 97% on room air. Differential diagnosis included infection, worsening polymyositis/interstitial fibrosis or pulmonary hypertension. Infection was excluded with a normal chest X-ray (CXR) and laboratory tests (Table 1). High-resolution CT chest was normal. Pulmonary hypertension was excluded on transthoracic echocardiography. A ventilation/perfusion scan excluded a pulmonary embolus.

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Table 1. Trend of laboratory investigations.

Laboratory results	Normal range	9 ⁺ weeks (at booking)	25 ⁺¹ (diagnosis of ICP)	26 ⁺⁶ (febrile illness)	27 ⁺⁵ (rifampicin added)	31 ⁺⁶ (at delivery)
White cell count ($\times 10^9/L$)	4.2–11.2	9.3		5.9	4.9	4.8
Platelets ($\times 10^9/L$)	135–400	393		286	343	75
Sodium (mmol/L)	133–146	135	126	130		125
Potassium (mmol/L)	3.5–5.3	3.6	3.8	3.8		3.6
Creatinine ($\mu\text{mol/L}$)	55–110	59	45	45		58
Bilirubin ($\mu\text{mol/L}$)	0–21	5	22	31	27	30
AST (IU/L)	0–40		59	157	158	169
ALT (IU/L)	0–40	20	41	71	82	16
Urine protein:creatinine ratio (mg/mmol)	<20		Not done		Not done	80
Creatinine kinase (IU/L)	25–200	50	200		210	517
Bile acids ($\mu\text{mol/L}$)	0–14	NA	79	105	95	117
Lactate dehydrogenase (IU/L)	125–243					1022
C-reactive protein (mg/dL)	0–5			5.1		

ALT: alanine transferase; AST: aspartate transaminase.

The rheumatologist prescribed 500mg methylprednisolone for a presumed exacerbation of her polymyositis due to a reduction in her prednisolone dose (4mg) by the enzyme-inducing effects of rifampicin.

Delivery was planned due to falling platelets, rising bile acids, ALT, BP and proteinuria (Table 1). An emergency Caesarean section was performed when she suffered a marked respiratory deterioration and spiked a temperature of 38°C.

Post-Caesarean section she remained intubated. Intravenous cefuroxime, metronidazole and oseltamivir were empirically commenced. On day 3, she developed frank haemoptysis and CXR showed new diffuse lower zone changes. Differential diagnosis included pulmonary haemorrhage secondary to her underlying connective tissue disease or infection. Amphotericin, ciprofloxacin, rifampicin, meropenem and cotrimoxazole were added, alongside plasmapheresis. Bronchoalveolar lavage revealed CMV of 24 million copies/ml. The CMV immunoglobulin M (IgM) that was initially negative, was positive on day 5 post-partum. Her CMV immunoglobulin G (IgG) was positive from virology samples stored from the start of pregnancy.

Due to her high oxygen requirements, she remained on venovenous extra-corporeal membrane oxygenation (ECMO) for 41 days. She developed abdominal collections that cultured mixed organisms, pancreatitis, recurrent upper gastrointestinal bleeds due to oesophagitis and a CMV-related duodenal ulcer, bilateral lower limb deep venous thrombosis and eventually trachea-oesophageal fistula. She died 137 days post-partum from respiratory failure secondary to an oesophageal tear from her fistula site. Her daughter remains well and free of CMV infection.

Discussion

Fifty to 80% of women of reproductive age show serological evidence of previous CMV infection.² The prevalence of CMV antibodies was 54.5% (n = 20,000 women) in three London antenatal clinics.⁴

Women with positive CMV IgG can still develop secondary CMV infection from reactivation or reinfection with a different strain.³ Women on immunosuppressive therapy are at higher risk of CMV infection.⁴ To diagnose primary infection, there should be evidence of seroconversion (defined as conversion from a negative to positive IgM or a four-fold increase in IgG antibody titre over a four- to six-week period). However, the accuracy of anti-CMV IgM to predict primary infection is complicated, as IgM antibodies can persist for months to years after primary infection and can be seen in cases of reactivation or reinfection.⁵

Congenital CMV can cause microcephaly, hepatosplenomegaly, chorioretinitis, intrauterine growth restriction and thrombocytopenia.⁶

In pregnancy, CMV often presents innocuously with a mild influenza-like illness, frequently accompanied by raised transaminases and low platelets. Acute CMV infection causes elevation of liver transaminase levels in about 92% cases.⁷ In contrast to other viral causes of hepatitis, in acute CMV infection, aspartate transaminase/ALT levels rarely go above five times the normal range.⁸ Pregnancy-specific differential diagnoses for a raised ALT in pregnancy are usually considered first and include either ICP or haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome. ICP is a diagnosis of exclusion, but few centres include CMV as part of routine testing.

It is possible that Mrs. T had a reactivation or reinfection with a new strain of CMV at the time of diagnosis of ICP; alternatively, this could have occurred when she presented with her febrile illness. It is also possible that HELLP syndrome in the peripartum interval with falling platelets was merely a reflection of worsening CMV after a bolus of 500mg IV methylprednisolone.

As increasing numbers of women receiving immunosuppression are attempting pregnancy, CMV should be included in the differential diagnosis when there is accompanying derangement in LFTs.

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MCS.

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