Acute herpes hepatitis in pregnancy

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Abstract
A 36 year old primigravid woman presented with a “flu-like” illness and premature labour, followed by severe pneumonitis and hepatitis in the late second trimester of pregnancy. Progressive deterioration obliged an elective delivery of twins, stillborn at 25 weeks of gestation. Herpes virus isolated from one placenta, but not from any fetal tissue, was the only indication of a systemic herpes simplex infection in which there were no mucocutaneous lesions seen before or during the illness. There was no history of herpes simplex infection and antibody studies were not helpful initially for a diagnosis that was confirmed in retrospect. Double staining for viral DNA and antigen showed that the virus was present in host monocytes.

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Case report
A 36 year old woman in the 24th week of a first and twin pregnancy was admitted to our obstetric unit with a 10 day history of shivers and fever, headache and myalgia, recurrent uterine contractions, and a vaginal discharge. These contractions and apparent dehydration, attributed to a “flu-like” illness, were corrected with terbutaline and intravenous fluids in her local hospital. After three days she developed an unproductive cough, with dyspnoea and moderate pain and tenderness in the epigastrium and right hypochondrium.

On examination in our obstetric unit, the patient was febrile (38.9°C) but initially quite well. Clear liquor was noted vaginally and she was admitted for observation. In the next two days the patient’s general condition declined, with cough, dyspnoea, and emerging upper abdominal pain. There was a developing tender enlarged liver of 10 cm, confirmed by ultrasound scan, a fever of more than 40°C and worsening blood gases of P02 7 kPa (53 mm Hg) and Pco2 3 kPa (24 mm Hg). Urea and electrolytes were within normal ranges, but the results of liver function tests were grossly abnormal (figure). A full blood count was normal except for a white cell count of 12.2 × 10^9/L with neutrophil leucocytosis. A plain chest X ray picture showed bilateral basal consolidation and linear atelectasis in the left mid-zone corresponding to perfusion scan defects. A working diagnosis of community acquired pneumonia with hepatitis was made, and treatment with intravenous cefuroxime (750 mg three times a day) and erythromycin (500 mg four times a day) started after blood was taken for culture and acute serology. As pulmonary embolism could not be excluded the patient was anti-coagulated with heparin. Ritodrine was given to suppress labour and dexamethasone was given in an attempt to mature the fetal lungs.

From days 2 to 6 after admission the patient’s condition continued to deteriorate: there were clinical and radiographic signs of confluent bilateral lower lobe consolidation, fever, hypoxaemia, and a steadily deteriorating liver function (figure). The prothrombin time ratio was 1.4 of normal. Myocarditis was seen on echocardiogram.

Blood cultures, respiratory secretions, and urine cultures were negative. The serum showed anticomplementary activity and this prevented any useful evaluation of all antibodies except herpes simplex (HSV) and varicella zoster viruses (VZV) (table 1) but a transient rise in EBV IgM and the presence of rheumatoid factor (also an IgM) was noted.

Six days after admission, erythromycin was discontinued because of the patient’s worsening liver function. In view of the severity of the illness, the pregnancy was terminated (day 8 after admission) by inducing a vaginal delivery with intravenous oxytocin and cervi-
cal prostaglandins. Both twins were stillborn after 24 hours. The placentae and fetuses looked normal. A brisk post partum haemorrhage required transfusion and a general anaesthetic for curettage. Following anaesthesia the patient remained on assisted ventilation for 36 hours (days 8–9 after admission). Radiographic chest signs initially deteriorated but then improved and hypoxaemia slowly improved in the days following delivery. After extubation the patient remained in a semiconscious state ranging from drowsiness to agitated confusion, but without any focal signs. Progressive oedema, moderate ascites, and a bilateral pleural effusion developed over the next four days (days 8–12 after admission) with a deterioration in liver function (figure). Repeat ultrasound scans showed pronounced hepatomegaly to the umbilicus with patent hepatic veins. Ascitic fluid contained monocytes, but unfortunately was not cultured for viruses and no bacteria were isolated. On day 13 (five days after delivery), the patient’s clinical state improved except for a fever of 38°C and an extremely tender and swollen liver. A computed tomography scan of the liver showed a pattern consistent with regeneration of liver architecture after severe parenchymal disease. As the clotting screen was abnormal, a liver biopsy was not undertaken.

The patient was discharged from hospital 37 days after admission and has made a recovery with the fevers resolving over three months, improving liver function, and normal liver size after six months. A liver biopsy specimen was taken two and a half months after the acute illness.

The necropsy examination of both fetuses and placentae, including histology, was entirely normal with no evidence of viral infection or cell inclusions. Histological evaluation of the maternal liver biopsy specimen taken two and a half months after the acute illness showed a normal architecture but residual chronic inflammatory infiltrates in some portal tracts. Occasional individual necrotic hepatocytes were present and the margin of one necrotic area showed a granulomatous reaction. No classic HSV inclusions were seen. Cubes of placenta and all major fetal tissues (2 cm) were disaggregated individually with sterile scissors in 2 ml viral transport medium and 8 drops of this medium were placed in a tissue culture tube containing MRC 5 cells incubated at 37°C. Herpes simplex virus type 2 (HSV 2) was isolated from one placenta only. No virus was isolated from any fetal tissues (table 2).

Double staining techniques1 to show both HSV 2 antigen and DNA were applied to the placenta from which HSV 2 was isolated and also to the liver biopsy specimen taken 2-5 months after the acute illness. Using tissue fixed in formol-saline or Carnoy’s reagent, dewaxed sections were digested with enzyme (protease VIII, Sigma Ltd, Poole, Dorset), exposed to a polyclonal HSV 2 antibody (Dako Ltd, High Wycombe, Buckinghamshire) and this was visualised with an anti-rabbit mouse antibody alkaline phosphatase conjugate and fast red. DNA hybridisation was carried out on the same sections using a 140 base pair fragment from the glycoprotein D gene common to both HSV 1 and HSV 2 as a double stranded diogyogenin labelled PCR produced probe. In the placenta maternal monocytes within lacunae stained for both HSV 2 antigen and DNA, indicating active virus replication. The trophoblastic tissue did not show any evidence of infection. In the liver biopsy specimen taken 2-5 months after the acute illness, discrete HSV 2 antigen and DNA staining was seen in occasional cells with poor correlation with the granulomatous areas and necrotic cells.

Discussion

Herpes simplex virus as a cause of severe systemic disease in pregnancy was first reported in 1969.3 There are eight reported cases, all occurring during the later second or third trimester, and all presenting with florid mucocutaneous herpes lesions. A series of discrepant changes in immune function during pregnancy is believed to allow systemic disease to develop.4-6 Mortality is estimated to be 40–50% in pregnancy7 and more than 80% for all herpes associated hepatitis.8

The clinical development of this case has similarities with the eight published cases of pregnancy associated disseminated herpes infection, reviewed in 1987.3 In our case a diagnosis was possible only in retrospect as there was no history or presentation of mucocutaneous lesions to suggest herpes infection. The limited evidence for a diagnosis of systemic herpes infection was virus isolation from one placenta (thought initially to be contamination during delivery), maternal monocytes in the placenta staining for viral products, and evidence of maternal liver infection 2-5 months after the acute illness. Serological data have not been diagnostic (see below and table 1). In a survey of 35 patients with systemic herpes infection, seven patients showed no signs of herpetic infection that would have been discovered during a thorough physical examination, although in some patients palatal lesions were recorded later.9 In our patient a cervical lesion could have remained unnoticed on first presentation.

An echocardiogram from our patient showed an myocarditis and an infiltration; this presentation has been reported before.9 We have no confirmed explanation for this or the pneumonic picture, which, in our case, was a presenting feature. Although a part of this cardiorespiratory pathology may have been viral replication within the affected tissues,

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<th>Table 2 Histological evidence for herpes simplex infection</th>
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<td>Fetal tissue Placental tissue Maternal monocytes Liver biopsy specimen</td>
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<td>HSV DNA</td>
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the rapid resolution of the pulmonary and cardiac problems suggests an indirect effect from rapid viral replication and viral antigen production within the liver. Hepatic virus replication may induce host cytokines and lymphokines, which would cause capillary permeability and fever and would account for a temporary worsening of the lung x ray picture after delivery, although function improved with assisted ventilation.

An encephalopathy with disseminated herpes infection in pregnancy has been described, and it has also been noted that the level of encephalopathy in a similar case was difficult to explain on the basis of abnormal liver function alone. In our case part of the encephalopathy developed after anaesthesia and was likely to be associated with severe liver metabolic impairment secondary to viral damage and also reflects opiate sedation under the same conditions. We had no evidence for a focal viral encephalopathy.

A rise in liver specific isoenzyme serum alkaline phosphatase after delivery (figure) was due to further rapid liver cell damage after the pregnancy had ended. This damage is likely to be caused by anaesthetic toxicity as well as some enhancement and synchrony in the immune recognition of infected cells after the end of pregnancy. Although Beer states that there is no convincing evidence for a general reduction in immune cell function (CMI) during pregnancy, there is evidence of an association between disseminated herpes infection and the gravid state. Others have suggested that a changed and restricted T cell function is essential to normal pregnancy, enhancing fetal tolerance, and in one study maternal lymphocyte immune response to phytohaemagglutinin was noted to be at its lowest during the 26th to 31st week of gestation. It has been suggested that gestation is associated with selective aspects of CMI depression and others have shown evidence that an attenuated T cell function, associated with normal pregnancy, may be a mechanism to facilitate systemic herpes infection.

In retrospect, the dexamethasone given shortly after admission in an attempt to mature the fetal lungs may have facilitated viral dissemination by further affecting T cell function. Longer term steroid treatment inhibits the normal function of circulating T cells and is observed to be associated with disseminated herpetic disease. If there had been any indication of the diagnosis on admission, steroids would have been appropriate only with antiviral treatment, although we do not believe that this or the terbutaline given during the first admission were responsible for initiating the developing disease.

The antibody changes observed during the acute illness did not provide a diagnosis; the mechanism for the observed antibody changes (table 1) is not clear. We could discount the raised VZV and HSV antibody titres in our patient as an indication of simultaneous first infection as there was a history of primary VZV infection in childhood. There was no VZV IgM present, although it is noted transiently in almost all cases of recrudescent infection (shingles); in immunosuppressed transplant recipients when there is VZV recrudescent disease we have noted the presence of VZV IgM in the serum and in the cerebrospinal fluid which would cause capillary permeability and fever and would account for a temporary worsening of the lung x ray picture after delivery, although function improved with assisted ventilation.

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responses in pregnancy and survival of fetal homograft. 


