Case report

Disseminated herpes simplex virus 2 as a complication of pregnancy

Lauren Bougioukas[a], Rachel B.C. Psoinos[a,b], David C. Jones[a,b,c], Erin A. Morris[a,b], Andrew J. Hale[a,b,*]

[a] Larner College of Medicine, University of Vermont, Burlington, VT, United States
[b] University of Vermont Medical Center, United States
[c] Fetal Diagnostic Center, United States

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ABSTRACT

Disseminated herpes simplex virus 2 (HSV-2) infection, is a rare but devastating infection in pregnancy women. We present the case of a 30-year-old gravida 3, para 2−0-0−2, at 26 weeks 2 days gestation who presented with eleven days of vague and indolent symptoms before a diagnosis of disseminated HSV-2 infection with associated hepatitis was made. While the patient clinically improved with empiric acyclovir treatment, possibility of significant harm to the fetus remained, and the patient request elective termination. The authors review the epidemiology, diagnosis, treatment, and prognosis of disseminated HSV-2 infection in pregnancy.

Introduction

Of the approximately 2–3% of women who acquire primary genital herpes simplex virus 2 (HSV-2) infection during pregnancy, the most dangerous complication is disseminated, systemic infection. With mortality rates up to 50 %, fortunately disseminated HSV-2 remains a rare entity [1–4]. Disseminated HSV-2 demonstrates an affinity for the second half of pregnancy, with 65 % of cases occurring in the third trimester; and an overall 50 % risk of transplacental infection [5–7]. Disseminated HSV-2 hepatitis during pregnancy may progress to fulminant liver failure and is a large contributor to maternal mortality approaching 50 % [8,9]. Acyclovir treatment poses minimal fetal risk and may significantly improve maternal clinical outcomes, although successful maternal therapy may not equate to successful fetal therapy [10,11]. Herein, we report the first elective mid-trimester termination in the setting of maternal disseminated HSV-2 disease with associated hepatitis.

Case

A 30-year-old gravida 3, para 2−0-0−2 presented to our tertiary care center at 26 weeks 2 days gestation with fever, malaise, shortness of breath, abdominal pain, and dysuria for the past eleven days. She denied significant past medical or surgical history, and her only medication was a prenatal vitamin. She had two prior uncomplicated term vaginal deliveries and denied any prior sexually transmitted infections.

She initially presented to a community emergency department at $24^{5/7}$ weeks with vaginal bleeding and was discharged following a normal pelvic exam. She next presented to our emergency department at $25^{1/7}$ weeks with a two-day history of urinary frequency and dysuria. She was afebrile and was discharged with empiric nitrofurantoin. At $25^{3/7}$ weeks, she presented to a second community emergency department with worsening malaise, abdominal and low back pain, and was discharged following a reassuring exam. She presented to the same emergency department at $25^{5/7}$ weeks with persistent symptoms. Rapid influenza and respiratory viral panel were negative, and she was discharged with a course of azithromycin for empiric pneumonia treatment.

At $26^{1/7}$ weeks gestation, she presented a third time to the community emergency department, now intermittently febrile up to 39.5 °C without localizing symptoms and was admitted for further evaluation. Speculum exam demonstrated clear vaginal fluid, which was nitrazine positive and negative for amniotic ferning. Serum studies were significant for transaminitis, which progressed from twice the upper limit of normal to an ALT of 200 U/L and AST 4of 20 U/L over a two-day admission, with normal total bilirubin. Pertinent negative infectious evaluation included influenza and respiratory syncytial viral (RSV) panels, viral hepatitis panel, urinalysis and culture, and blood cultures. Abdominal magnetic resonance imaging (MRI) and right upper quadrant

* Corresponding author at: University of Vermont Medical Center, Infectious Disease Unit, 111 Colchester Avenue, Mailstop 115 SM2, Burlington, VT, 05401, United States.
E-mail address: Andrew.Hale@UVMhealth.org (A.J. Hale).

ultrasound were unrevealing. She received empiric therapy with piperacillin-tazobactam and was discharged within 24 h.

The following day, the patient presented to our tertiary care facility at $26^{2/7}$ gestation, complaining of chills, malaise, fever to 39.4 °C, new onset of shortness of breath, dry cough, headache, and copious vaginal discharge over the prior three days. Upon arrival, she was febrile to 39.2 °C, tachycardic to 121 beats per minute, and normotensive with normal oxygen saturation. Physical exam elicited exquisite umbilical, suprapubic, and left flank tenderness. Sterile speculum exam revealed copious thick yellow vaginal fluid and scant pinpoint white cervical lesions, both of which were swabbed for culture and viral polymerase chain reaction (PCR). Vaginal fluid was nitrazine positive; however, microscopy did not reveal amniotic ferns, lowering the suspicion for premature rupture of membranes. The cervix was closed and there was no evidence of active labor. Obstetric ultrasound confirmed a viable fetus with biometry consistent with prior dating. Anatomic survey was normal.

Admission laboratory studies were remarkable for worsening transaminitis compared to her prior admission, with ALT 265 U/L and AST 602 U/L, with total bilirubin 1.1 mg/dl. Complete blood count showed WBC $5.36 \times 10^3/mm^3$ with 10.6 % banded neutrophils. Hemoglobin was 10.5 gm/dL, hematocrit was 28.5 %.and creatinine was 0.42 mg/dL. Serum C-reactive protein was elevated at 265.2 mg/L. Urinalysis was significant for moderate ketonuria and leukocyte esterase, many squamous cells and leukocytes, few erythrocytes, and no bacteriuria. Hepatobiliary ultrasound was unremarkable.

The patient's exposure history was significant for work in a daycare setting and cat ownership. Additionally, the father of the current pregnancy engaged in recent non-monogamous activity. Due to maternal and neonatal acuity as well as refractory symptoms and clinical status, prompt ultrasound-guided amniocentesis on day of admission evaluated for intraamniotic infection (IAI). Indigo carmine intraamniotic infusion and tampon test were negative, confirming intact amniotic membranes. Rapid testing of amniotic fluid revealed manual leukocyte count of 16 cells/cmm, and fluid glucose of 22 mg/dL, with present neutrophils and absent bacteria, felt to be most consistent with a viral IAI, though bacterial etiology was not dismissed.

Due to the concern for IAI, on hospital day one empiric intravenous ertapenem (1 g daily) and oral azithromycin (500 mg daily) were initiated. Worsening transaminitis through hospital day two (ALT 302 U/L, AST 714 U/L) was initially attributed to sepsis secondary to IAI. The patient's serum INR and mental status remained normal.

Pertinent negative maternal testing included influenza A/B and respiratory syncytial virus nasopharyngeal PCR, serologies for toxoplasma, cytomegalovirus (CMV), and syphilis, Mono-spot, and HIV screening. Urine culture, chlamydia and gonorrhea PCR, and vaginal Group B Streptococcus PCR were negative. Blood and amniotic fluid cultures for aerobic and anaerobic bacteria demonstrated no growth.

Later on hospital day two, HSV-2 PCR of a cervical lesion returned positive and she was started on intravenous acyclovir (10 mg/kg every 8 h). She denied prior oral or genital symptoms or knowledge of HSV-2 infection. As her partner endorsed a history of recent multiple sexual partners, a primary HSV-2 infection was suspected. On hospital day three, HSV-2 PCR of amniotic fluid and serum also returned positive, consistent with disseminated HSV-2 infection with associated hepatitis and suspected congenital infection of the fetus.

Ertapenem and azithromycin were discontinued. After 24 h of acyclovir therapy, her fever resolved, and transaminitis began to down trending. By hospital day four, transaminitis began to resolve, there was no evidence of hepatic synthetic dysfunction or hepatic failure, and she thereafter remained consistently afebrile.

While the patient clinically improved after diagnosis and initiation of targeted therapy, she had ongoing concerns about the fetal and neonatal implications of her diagnosis, and ultimately, she requested pregnancy termination. A multidisciplinary care team, including Maternal Fetal Medicine, Clinical Ethics, and Infectious Disease, was assembled to review the patient's desire for termination, as well as fetal implications of HSV-2 positive amniotic fluid. The committee determined there was reasonable possibility of significant fetal harm due to maternal primary disseminated HSV-2 infection with evidence of transplacental transmission. The patient ultimately elected to terminate the pregnancy.

Feticide was performed by ultrasound-guided intracardiac injection of potassium chloride on hospital day seven, at 27 weeks 1 day. Upon confirmation of fetal demise, induction of labor was performed by administration of mifepristone, followed by high dose misoprostol, according to Society of Family Planning published practice guidelines [12,13]. During her labor course, she developed pre-eclampsia without severe features. After a three-day induction, the patient delivered a demised male fetus.

Placental histopathology was significant for high grade fetal vascular malperfusion, acute chorioamnionitis and funisitis, focal chronic chorionic plate vasculitis, and necrotic stromal cells. While there was no evidence of viral cytopathic effect and HSV-2 immunostaining was negative, intradepartmental review determined the findings to be consistent with transplacental HSV-2 infection in the setting of disseminated maternal disease. Fetal autopsy was declined by the patient.

The patient was discharged on hospital day ten, shortly after delivery. She was transitioned to oral valacyclovir 1 g every 8 h, to complete a 21-day total course. Upon outpatient follow-up she remained afebrile with complete resolution of transaminitis and no evidence of hepatic dysfunction.

Discussion

As illustrated here, the diagnosis of disseminated HSV-2 infection during pregnancy can be challenging. Women frequently report no history of HSV-2 infection, and characteristic herpetic lesions may be absent. Providers frequently consider a broad differential, including pre-eclampsia and acute fatty liver. Definitive diagnosis by liver biopsy can be difficult in the pregnancy setting, especially if hepatitis has progressed to a coagulopathic state. Although treatment with acyclovir can result in a successful maternal outcome, disseminated HSV-2 in pregnancy is an overall highly morbid disease for both mother and fetus, and the effect of acyclovir on the fetus remains unclear [10,11,14–16].

This is borne out in a disseminated HSV-2 case described by Sloan et al. in which second trimester maternal therapy was initially reassuring; however, third trimester fetal ultrasound revealed severe cerebral findings consistent with encephalitis and ultimately neonatal demise [17]. Johansson et al. describe a patient with a self-resolving first trimester flu-like illness, who delivered a preterm neonate severely affected by classic and non-classic constellation of congenital HSV-2 sequelae [18]. This presents in stark contrast to those cases that report successful maternal and neonatal outcomes with acyclovir treatment [14,19–23]. While the advent of PCR testing for HSV-2 in amniotic fluid is a useful tool confirming maternal diagnosis in addition to viral culture, neither has been demonstrated to clearly correlate with reduced neonatal morbidity [20,24].

Neonatal HSV-2 infection affects an estimated 1500 live births annually in the United States with substantial resource utilization [25–27]. Attempts have been made to characterize a classic triad of neonatal presentation including central nervous system, ophthalmologic, and cutaneous involvement, however in cases of

intrauterine infection, congenital HSV does not appear to be limited to these manifestations, comprising a spectrum including extremity and bony malformations, altered growth, hydrops, cerebral abnormalities, and fetal demise [28–30]. In a review of 64 cases of intrauterine HSV infection diagnosed prenatally and postnatally, cutaneous lesions were identified in 95 % of cases, while CNS abnormalities were identified in 67 % cases [28]. In 36 cases of congenital HSV infection, 15 were described prenatally, with cerebral anomalies the most commonly reported, and 21 were diagnosed postnatally, most commonly with cutaneous findings that developed in the first weeks of life [29]. Fetal diagnostic imaging including ultrasound and MRI have limited utility in successfully identifying cutaneous manifestations, which can be extensive, as well as determining neurodevelopmental prognosis, as normal anatomic survey does not guarantee a normal neonatal outcome [29,31].

Early diagnosis of disseminated HSV in pregnancy with acyclovir treatment is often delayed, yet critical in improving maternal outcomes. The literature demonstrates that maternal treatment and reassuring fetal imaging do not guarantee a normal neonatal outcome [17,18]. While intrapartum demise and with-holding or withdrawal of supportive care in the immediate postnatal setting have been described in clearly affected neonates [28], this is the first report of an elective mid-trimester induction termination in the setting of maternal disseminated HSV-2 hepatitis.

Author contributions

Lauren Bougioukas, BA: conceptualization, patient care, writing: original draft; writing: review & editing

Rachel B.C. Psoinos, MD, PhD: conceptualization, patient care, writing: original draft; writing: review & editing

David C. Jones, MD: conceptualization, patient care, writing: original draft; writing: review & editing

Erin A. Morris, MD: conceptualization, patient care, writing: original draft; writing: review & editing

Andrew J. Hale, MD: conceptualization, patient care, writing: original draft; writing: review & editing

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Informed consent

Written informed consent was obtained from the patient

Declaration of Competing Interest

The authors declare no conflict of interest.

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