Antiviral-Resistant Fulminant Herpes Hepatitis in Pregnancy

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Abstract

Fulminant herpes hepatitis with disseminated extrahepatic involvement in pregnancy is rare and carries a high mortality risk. Although acyclovir remains standard first-line therapy, effective management of acyclovir-resistant disseminated herpes simplex virus (HSV) in pregnancy remains elusive. We present a case of disseminated HSV resistant to both acyclovir and foscarnet, the first double-agent resistant case in pregnancy reported in the literature to date. In this case, therapeutic delivery was the ultimate treatment resulting in full recovery.

Keywords
► herpes hepatitis
► fulminant herpes
► pregnancy herpes
► disseminated herpes

Fulminant herpes simplex virus (HSV) hepatitis with disseminated extrahepatic involvement is a rare complication of herpes virus infection, traditionally described in significantly immunocompromised hosts.1 The immunosuppressive effects of pregnancy make pregnant women the second most common population to suffer from disseminated disease.2 Humoral and cell-mediated immunity are most depressed in the third trimester, as demonstrated by decreased T-cell count and altered B-/T-cell ratios.2 Disseminated disease is life-threatening, with maternal mortality risk reported to be as high as 39%.2 The current treatment recommendation for fulminant HSV hepatitis in pregnancy is intravenous (IV) acyclovir, with the addition of foscarnet for acyclovir-resistant cases.3 We present a case refractory to both acyclovir and foscarnet, the first of its kind reported in the literature.4 Ultimately, only delivery resulted in resolution of maternal hepatic and neurologic dysfunction.

Case Report

The patient was a 24-year-old gravida 1 with no significant medical history who presented to our hospital as a transfer of care at 27\(\frac{2}{7}\) weeks' gestation with fever of unknown origin, hepatic failure, and leukopenia. She presented to the outside facility 7 days prior with vague complaints of fever, nausea, abdominal pain, malaise, and anorexia. At the outside hospital, she was noted to have mild transaminitis (alanine transaminase [ALT] 205 U/L, aspartate transaminase [AST] 357 U/L) and persistent fevers. Empiric broad-spectrum antimicrobial coverage was initiated, including azithromycin, piperacillin/tazobactam, and acyclovir. Initial laboratory evaluation included negative blood cultures and hepatitis panel. Additionally, antibody testing was negative for rapid plasma reagin (RPR), human immunodeficiency virus, rubella, toxoplasma, streptococcus pneumovirus, influenza A/B, respiratory syncytial virus (RSV), parainfluenza, legionella, chlamydia, gonorrhea, and antinuclear antibody (ANA). Epstein-Barr virus testing was consistent with remote infection. Due to continued fevers, hypoxemia, a new chest consolidation, and worsening liver failure with associated coagulopathy, the patient was transferred to the medical intensive care unit (MICU) at our facility on hospital day 7.

Upon arrival to our MICU, physical exam was significant for mild jaundice and a few very small shallow, friable ulcerations on the labia. We obtained HSV cultures and continued broad-spectrum antibiotics with IV acyclovir from the outside facility. Despite supportive care and appropriate antimicrobial therapy, the patient's hepatic dysfunction worsened (AST 2290 U/L, ALT 783 U/L, lactate dehydrogenase 6551 U/L, and total bilirubin 7.5 mg/dL) with associated...
coagulopathy (international normalized ratio [INR] 1.9). On
day hospital day 8, she developed significant pancytopenia,
hypotension requiring dual-agent pressor therapy, and acute
respiratory failure requiring intubation. She had significantly
altered mental status concerning for hepatic encephalopathy
versus herpetic encephalitis. We diagnosed disseminated
extrahepatic HSV 2 with associated fulminant hepatitis by
polymerase chain reaction (PCR) in genital, liver, bronchoal-
veolar, blood, and cerebral spinal fluid samples. Given the
lack of clinical response to acyclovir and a plateau in maternal
serum HSV PCR cycles, the consulting infectious disease
specialists recommended the addition of foscarnet as sec-
ond-line therapy for treatment of acyclovir-resistant HSV
hepatitis on hospital day 21.

Of note, initial fetal anatomic survey at the outside hospital
was consistent with an isolated open-lipped schizencephaly.
After extensive counseling by the maternal fetal medicine
providers there, the patient opted for palliative care with no
fetal monitoring or intervention. The fetal diagnosis was
confirmed via ultrasound at our institution. Prior to intuba-
tion and mental status change, the patient had again con-
ﬁrmed her strong desire for no intervention on behalf of the
fetus.

On hospital day 24, the patient remained neurologically
impaired, intubated with increasing ventilator requirements,
hypotensive, and coagulopathic. Given the lack of response
to dual-agent antiviral therapy, rising maternal serum lactate
levels (11.2 mmol/L), and very guarded prognosis, we held a
multidisciplinary conference to discuss the potential thera-
peutic beneﬁt of delivery. Due to the prenatal diagnosis of
schizencephaly and desire for no fetal intervention, as well as
worsening maternal status, we made the decision to proceed
with prostaglandin induction via misoprostol (50 µg every 6
hours). In planning for induction, we performed a fetal
paracentesis due to a new finding of fetal ascites and concern
for abdominal dystocia during delivery. HSV PCR on the fetal
fluid returned negative. On hospital day 25, a female fetus was
delivered vaginally with no signs of life weighing 1,878 g.
Fetal autopsy was declined by the patient’s health care
surrogate.

The patient’s immediate postpartum course was compli-
cated by transient hypophysinomenia concerning for dis-
seminated intravascular coagulopathy. We placed an
intrauterine balloon for 36 hours secondary to postpartum
hemorrhage, which was thought to be due to coagulopathy
and not related to uterine atony. The coagulopathy was
resolved with factor replacement and red cell transfusion.
Within 4 days of delivery, the patient was successfully
extubated, weaned off pressor support, and had signiﬁcant
improvement in hepatic function marked by normalizing
transaminases, total bilirubin, and INR. Her encephalopathy
resolved more slowly, but normal mental status was noted
before ﬁnal discharge to home on hospital day 44. Repeat HSV
PCR from blood sampling remained positive at time of
discharge, but continued to trend downward. She remained
on acyclovir for the duration of her hospital course and will
need a prolonged outpatient course per recommendations
from infectious disease specialists.

Discussion

Fulminant herpes hepatitis is rare, with the disease burden
heavily concentrated among neonates and severely malnour-
ished children. In 1969, Thomas Henry Flewett, a prominent
British pathologist, and colleagues reported the ﬁrst adult
case in a female patient at 28 weeks’ gestation who developed
hepatic dysfunction following primary herpetic stomatitis.5
Since that time, 34 more cases of herpes hepatitis in preg-
nancy have been reported in the literature, with a mortality
rate of 39% reported by Kang and Graves in 1999, but only 9%
among the subsequent 11 cases reported from 2000 to
present6–14 This is in stark contrast to the 74.4% mortality
rate for herpes hepatitis in the general population reported by
Norvell et al in 2007 and may reﬂect the underlying disease
state that made the nonpregnant patients vulnerable to
disseminated herpes.15

The nomenclature used to describe variations of systemic
herpes infections is applied inconsistently throughout the
literature. For the purpose of our work, disseminated herpes
refers to HSV documented by culture or PCR in a nongenital or
mucosal fluid or tissue. Herpes hepatitis is more speciﬁc and
describes patients with seropositive active herpes viremia
(usually measured via serum PCR) and associated transami-
nititis. Fulminant herpes hepatitis includes HSV-seropositive
patients with true liver failure (as evidenced by decreased
albumin, elevated INR, and severe transaminitis) in critical
condition. Our case describes a patient with fulminant herpes
hepatitis, the most severe form of the infection.

The clinical presentation of febrile abdominal pain and
anicteric hepatic dysfunction in pregnancy should prompt
immediate consideration of the diagnosis of herpes hepatitis
and separates this disorder from the other common etiologies
of nonfebrile hepatic failure in pregnancy: acute fatty liver,
preeclampsia/HELLP (hemolysis, elevated liver enzymes, and
low platelets), and intrahepatic cholestasis. Clinical symp-
toms concerning for disseminated herpes can be nonspeciﬁc,
including fever, malaise, abdominal pain, and nausea. Labo-
ratory ﬁndings, too, can be subtle in the early stages, includ-
ing mild transaminitis, leukopenia, and elevated INR. The gold
standard for the diagnosis of herpes hepatitis remains liver
biopsy with histopathology, electron microscopy, and culture.
The classic ﬁnding of hemorrhagic necrosis, inﬂammation,
and enlarged ground glass nuclei with marginalized chroma-
tin is pathognomonic.16 However, percutaneous liver biopsy
in the setting of maternal coagulopathy can be associated
with signiﬁcant bleeding-related morbidity, making alterna-
tive deﬁnitive diagnostic modalities desired. Basic serology
carries a well-known risk of false negative result; PCR assay
from a maternal serum sample should be performed in such
cases where the diagnosis remains suspected.12,14 If the
testing is positive, clinicians can follow serial PCR ampliﬁ-
cation crossing points, which correlate with viral load (the
higher the cycle number, the lower the viral quantity), to
determine the persistence and strength of viremia (–Fig. 1).

Though no antiviral agent has been proven effective in
randomized trials, intravenous acyclovir is standard ﬁrst-line
therapy for presumed disseminated disease. In cases of
drug-resistant herpetic infection, intravenous foscarnet is the agent of choice but carries with it a significant risk of toxicity to the renal tubules. A pyrophosphate analogue that selectively inhibits viral polymerase, foscarnet is primarily used to treat cytomegalovirus when ganciclovir is contraindicated, as well as acyclovir-resistant herpes virus or varicella zoster. Though no adverse events have been reported with foscarnet use in pregnancy, the data are sparse, and current recommendations are for use only in the setting of a high risk of maternal mortality without treatment. 

Despite intensive supportive care and treatment with both acyclovir and foscarnet, our patient experienced progressive multiorgan dysfunction and persistent stable viremia as measured by serum qualitative HSV PCR, the first case of dual-agent resistance to be reported. When traditional intravenous antiviral therapies failed and progression appeared very poor, a multidisciplinary team offered the patient’s family the option of therapeutic induction of labor, with the caveat that the third trimester. In summary, the diagnosis of herpes hepatitis and empiric treatment with intravenous acyclovir should be strongly considered in any case of febrile hepatic dysfunction in pregnancy. We recommend consideration be given to therapeutic delivery in the setting of antiviral-resistant disease with concern for maternal mortality; we also suggest that HSV qualitative PCR be used to trend disease burden.

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