# 41-Year-Old Woman With Fever, Neutropenia, and Elevated Transaminase Levels

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A 41-year-old woman presented to our institution with fever. She had been recently diagnosed as having stage I invasive ductal carcinoma of the breast, which was managed with wide local excision followed by adjuvant chemotherapy with docetaxel and cyclophosphamide. She presented to her local hospital 4 days after her second cycle of adjuvant chemotherapy with fever and sore throat but was discharged after rapid streptococcus test and blood culture results were negative. On presentation to our hospital the following day, her blood pressure was 127/65 mm Hg, but she was febrile (temperature, 39.4°C). She had tachycardia (126 beats/min), tachypnea (22 breaths/min), and neutropenia, with a leukocyte count of $0.8 \times 10^9$/L and an absolute neutrophil count (ANC) of $0.25 \times 10^9$/L. Preliminary testing for an infectious source in the lungs, urine, and blood yielded negative results.

1. **Which *one* of the following is the *most appropriate* next step for management of this patient's condition?**
   a. Discharge with close follow-up
   b. Admit to the hospital and start intravenous (IV) meropenem and granulocyte colony-stimulating factor
   c. Admit to the hospital and administer IV vancomycin and cefepime
   d. Outpatient management with oral ciprofloxacin and amoxicillin-clavulanate
   e. Admit to the hospital and initiate IV cefepime and levofloxacin

The patient's presentation is characteristic of neutropenic fever (temperature >38.3°C or >38.0°C sustained over an hour in a patient with an ANC of $0.5 \times 10^9$/L or an expected nadir of $0.5 \times 10^9$/L within 48 hours). Discharging the patient without administering antimicrobial therapy is inappropriate. Although meropenem is adequate to cover gram-negative organisms including *Pseudomonas* in patients with neutropenic fever, granulocyte colony-stimulating factor is not generally recommended for treatment of neutropenic fever.[1] Admission to the hospital and administration of cefepime is appropriate because it covers most gram-negative organisms associated with neutropenic fever as well as *Streptococcus* species and methicillin-sensitive *Staphylococcus aureus*; however, adding vancomycin to the regimen at this stage is not recommended unless methicillin-resistant *S aureus* infection is documented or strongly suspected, if the patient was previously taking prophylactic antibiotics, or if a central venous line infection is suspected.[1] If the patient was otherwise stable, outpatient management with ciprofloxacin and amoxicillin-clavulanate would be appropriate. However, our patient had tachypnea and tachycardia; therefore, outpatient management would be inappropriate because of her risk of decompensation. Hospital admission and initiation of a combination of cefepime and levofloxacin is the best choice because it would empirically cover gram-positive and gram-negative organisms including *Pseudomonas*, as well as provide coverage for other atypical organisms.

The patient's fever (as high as 39.6°C), tachycardia (up to 139 beats/min), and tachypnea (up to 40 breaths/min) persisted for 9 days in a cyclic pattern even after neutropenia resolved (within 4 days after a nadir ANC level of $0.22 \times 10^9$/L ). Her blood pressure remained within normal limits. Metronidazole and vancomycin were added, but bacterial blood culture results remained negative. With no improvement, caspofungin was added and levofloxacin was discontinued. Because of concern about a drug-induced fever, all antimicrobial agents were eventually discontinued with the exception of caspofungin and the addition of meropenem. On hospital day 4, the patient complained of right upper quadrant (RUQ) abdominal tenderness. She also had oral lesions with a whitish

**See end of article for correct answers to questions.**

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gelatinous-appearing exudate on her hard palate, tongue, and the corner of her mouth. Laboratory investigation revealed rapidly increasing aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels (reference range, 7-45 U/L), which eventually peaked at 1701 U/L (reference range, 8-43 U/L) and 871 U/L, respectively. The bilirubin level peaked at 0.8 mg/dL (reference range, 0.1-1.0 mg/dL). Because we were concerned about a drug adverse effect, caspofungin was discontinued.

**2. In view of the findings thus far, which *one* of the following is the *most likely* cause of the elevated transaminase levels and fever in this patient?**

a. Liver metastases
b. Caspofungin toxicity
c. Acute viral hepatitis
d. Invasive fungal infection
e. Ischemic hepatitis

Acute liver failure secondary to metastatic infiltration is possible but rare and can be considered if a patient with cancer experiences marked hepatomegaly and signs of fulminant hepatic failure.[2] However, in the context of this patient's stage I disease, this is not the most likely cause of transaminase elevations. In general, caspofungin has a favorable adverse effect profile compared with other antifungal agents used for treatment of invasive fungal infections; liver enzyme derangements are typically mild and do not lead to serious liver injury.[3] Acute viral hepatitis is the most common cause of acute liver injury worldwide.[4] Patients may present with fever, RUQ abdominal pain, jaundice, and malaise; therefore, acute viral hepatitis is the most likely cause of the patient's symptoms and laboratory findings. If patients with neutropenic fever do not improve after aggressive antibiotic treatment, invasive fungal infections are often suspected. However, fungal infections are less likely in patients who have not had severe (neutrophil count $<0.5 \times 10^9$/L) and prolonged ($\geq$7 days) neutropenia.[5] Our patient did have marked neutropenia (nadir, $0.22 \times 10^9$/L), but she was only neutropenic for 4 days, and therefore invasive fungal infection is unlikely. Ischemic hepatitis, commonly referred to as *shock liver*, is a cause of markedly elevated transaminase levels. However, it typically occurs after decreased hepatic blood flow and hypoxemia, usually in the setting of underlying right-sided heart failure.[6] These conditions did not exist in our patient, making ischemic hepatitis unlikely.

Hepatic ultrasonography showed diffuse fatty infiltration of the liver. Serologic analysis was negative for hepatitis A, B, and C, Epstein-Barr virus, cytomegalovirus, $\alpha_1$-antitrypsin deficiency, Wilson disease, autoimmune hepatitis, fungal or atypical bacterial infections, and acetaminophen. In view of the oral lesions and the appearance of hepatic inflammation on ultrasonography, herpes simplex virus (HSV) viremia was suspected and believed to be disseminated, causing HSV hepatitis.

**3. Which *one* of the following is the *best* confirmatory test for this patient's suspected diagnosis?**

a. Liver biopsy
b. Serum HSV polymerase chain reaction (PCR)
c. HSV viral cultures
d. Serum HSV antibodies
e. Tzanck smear

The criterion standard for diagnosis of HSV hepatitis is liver biopsy with PCR or immunohistochemical examination of tissue.[7] However, a liver biopsy is not desirable in patients who are already immunocompromised or have bleeding or clotting disorders secondary to cancer. Serum HSV PCR is a safer noninvasive tool and a good second choice, often providing faster results.[7] Therefore, it is the most appropriate confirmatory test in this case. Viral cultures have very low yield and are time consuming. Because HSV hepatitis is usually a result of reactivation of HSV infection, serum HSV antibodies are not a reliable confirmatory test. The Tzanck smear is an older test in which staining a sample from the base of a herpetic lesion can reveal characteristic multinucleated giant cells. This is not useful in diagnosing HSV viremia or hepatitis.

Biopsy was considered, but the blood HSV PCR was positive for HSV type 1, confirming the diagnosis of disseminated HSV and HSV-associated hepatitis. Meropenem was discontinued and HSV-directed treatment was


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initiated immediately with doses adjusted as appropriate.

4. **For the initial treatment of this patient's condition, which *one* of the following is *most appropriate*?**
   a. Fluids and rest because HSV hepatitis is a self-limited disease
   b. Oral valacyclovir
   c. Oral acyclovir and prednisone
   d. IV acyclovir
   e. Liver transplant

In immunocompetent hosts, HSV infection is usually self-limited, resulting in mucocutaneous involvement and nerve ganglion latency, and therefore can be treated with fluids and rest. However, it would not be appropriate in our patient, who is immunocompromised due to her chemotherapy. Valacyclovir has efficacy against herpetic viruses similar to that of acyclovir but is more expensive, and in the initial treatment phase of HSV hepatitis, oral antiviral agents are not a good choice. Prednisone has not been shown to increase the efficacy of acyclovir and may in fact worsen the clinical outcome. High-dose IV acyclovir (10 mg/kg every 8 hours) is the best initial treatment for HSV hepatitis.[8] Liver transplant is often an end point of fulminant hepatic failure, but in this patient's situation it would be premature.

After initiation of appropriate treatment, the patient's fever, RUQ tenderness, and abnormal transaminase levels immediately improved.

5. **Which *one* of the following statements about this patient's long-term management is *true*?**
   a. She will always be at risk for recurrence
   b. No further monitoring is necessary
   c. She is at increased risk for hepatocellular carcinoma
   d. Her treatment has a benign adverse effect profile
   e. She now requires lifelong treatment

The patient will always be at risk for recurrence of HSV infection because it lies dormant in nerve ganglia until another episode of immunosuppression. Although the condition resolved clinically, close monitoring after discharge is necessary to ensure that her liver enzyme levels normalize completely and that she does not have relapse or development of serious adverse effects. There is no evidence to show that this patient, having had HSV hepatitis, is now at increased risk of hepatocellular carcinoma. Patients who receive high-dose IV acyclovir require close monitoring with weekly measurement of serum creatinine concentrations because they are at risk for acute renal failure. Although our patient's physician may choose to prescribe acyclovir-valacyclovir prophylaxis during chemotherapy cycles, the Infectious Diseases Society of America guidelines currently only recommend lifelong HSV prophylaxis in patients who have undergone hematopoietic stem cell transplant or are receiving urgent induction or reinduction chemotherapy for acute leukemia.[1]

After being afebrile for 72 hours, the patient was discharged with a recommendation for close follow-up and a prolonged course of antiviral treatment. At discharge, her AST and ALT values were 62 U/L and 181 U/L, respectively. She and her oncologist elected to discontinue chemotherapy, given her relatively low risk of cancer recurrence and the high risk of chemotherapy-related infectious complications.

## DISCUSSION

Our case emphasizes the importance of including rare causes of hepatitis in the differential diagnosis when evaluating immunocompromised patients. The most common cause of acute severe hepatitis worldwide is viral hepatitis.[4] Viruses most commonly implicated include hepatitis viruses A, B, C, and E, cytomegalovirus, Epstein-Barr virus, parvovirus, and HSV are also known to cause symptomatic hepatitis and are more likely to result in fatal or near-fatal outcomes among immunocompromised hosts. In immunocompromised patients, reactivation of HSV can lead to life-threatening viremia and visceral disease. The populations most commonly affected include transplant recipients, pregnant women, and those undergoing chemotherapy.[9] However, cases have been documented in immunocompetent patients.[9] In our patient, HSV viremia was a result of viral reactivation associated with episodes of asymptomatic cold sores that the patient later reported had occurred before initiation of chemotherapy.

The patient's prognosis remained guarded throughout her hospitalization, although it improved when she received IV acyclovir. In cases of fulminant hepatic failure, mortality approaches 80%.[10] Diagnosis of HSV hepatitis is often made post mortem due to delay in diagnosis.[11] Nonspecific symptoms (including fever, malaise, and RUQ tenderness), absence of herpetic lesions, or confounding history and physical examination findings can lead to premature closure before considering all possible diagnoses and delay in diagnosis if the treating physician considers a narrow differential diagnosis. In addition, herpes labialis is a common lesion among immunocompromised hosts, making it hard to use as pathognomonic evidence of HSV hepatitis, although this finding is helpful if HSV hepatitis is already suspected. Our patient initially seemed to have a typical case of neutropenic fever of unknown origin until hypertransaminasemia, oral lesions, and RUQ tenderness developed several days after her hospitalization. Hypertransaminasemia in HSV hepatitis is known as *anicteric hepatitis*, characterized by marked elevation in AST and to a lesser extent in ALT levels and low or normal bilirubin values.[9]

Timely diagnosis and treatment are the keys to preventing mortality in this disease. With treatment, the prognosis remains guarded, even in immunocompetent patients.[12] Results of traditional serologic analyses are often nonspecific, and the time required for viral cultures may delay diagnosis. The criterion standard for diagnosis is a liver biopsy, which will reveal pathognomonic eosinophilic intranuclear hepatocellular inclusions called *Cowdry bodies*.[7] Special immunohistochemical staining and PCR of hepatocyte nuclei will be positive for HSV. Unfortunately, bleeding risks associated with this procedure in immunocompromised or pregnant patients often outweigh the diagnostic benefits. Real-time serum PCR has been proven to be a rapid, accurate, noninvasive alternative to liver biopsy, but it is not available at all medical centers.[7] In our patient, PCR made the diagnosis possible within a few hours of performing the test, allowing us to initiate prompt, appropriate treatment with high-dose IV acyclovir. This case highlights the importance of a thorough history and physical examination for rapid diagnosis and swift initiation of treatment.

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**CORRECT ANSWERS: 1. e. 2. c. 3. b. 4. d. 5. a**