Case report

Empirical treatment with parenteral acyclovir in a child with herpes simplex virus hepatitis and acute lymphoblastic leukemia

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ABSTRACT

Introduction: Hepatitis secondary to Herpes Simplex Virus (HSV) infection is a complication that often leads to fatal hepatic failure. Early treatment with the anti-viral drug, acyclovir, is life-saving. In view of the non-specific nature of the signs and symptoms associated with HSV hepatitis, diagnosis is often made late during the course of the disease; a factor that largely contributes to the high mortality rate of this treatable disease complication. There is thus a growing consensus in the field to initiate empirical treatment with acyclovir once suspicion of HSV hepatitis is raised even before reaching a conclusive diagnosis.

Presentation of case: We present clinical evidence on the benefit of starting empirical acyclovir treatment on the outcome of patients suffering from HSV hepatitis. We report two cases of HSV hepatitis in children with cancer. One case presented with fulminant hepatitis which was fatal and the diagnosis was only reached post mortem. In the second case, there was enough suspicion of HSV hepatitis to start early empirical acyclovir therapy. The diagnosis was confirmed 48 hours following the initiation of treatment and the early intervention with anti-virals proved to be life-saving.

Discussion: In both cases above, the following symptoms were shared; fever, elevated transaminase levels and mucositis without clear cutaneous lesions. HSV hepatitis should thus be considered in the differential diagnosis of immunocompromised patients exhibiting the above symptoms.

Conclusion: Due to the frequent delay in HSV diagnosis and the safety of acyclovir, we recommend empirically administering acyclovir in patients suspected of HSV hepatitis.

Introduction

Herpes simplex virus (HSV) hepatitis is an uncommon complication of HSV infection and is a cause of fatal hepatic failure [1]. Current statistics indicate that neonates, the immunocompromised and pregnant females constitute the majority of affected individuals; however, several cases were reported in otherwise immunocompetent patients [2–4]. Early acyclovir therapy is often life-saving [5,6]. Unfortunately, the lack of specific signs and symptoms delays the diagnosis and contributes largely to the high observed rate of morbidity and mortality [6]. Based on the above, there is adequate rationale to initiate empirical acyclovir therapy whenever there is suspicion of HSV hepatitis. This, however, requires evidence based testing to establish clear clinical guidelines of when to initiate empirical acyclovir.

Herein, we report two cases of HSV hepatitis in children with Acute Lymphoblastic Leukemia (ALL). One case presented with fulminant hepatitis which was fatal and the diagnosis was only reached post mortem. In the second case, there was early suspicion of HSV hepatitis and empirical acyclovir therapy was administered. The diagnosis was confirmed 48 hours following the initiation of treatment. Early introduction of acyclovir proved to be life-saving.

Case

Case 1

A 2.5 year old male patient with pre-B ALL in remission. He had a smooth consolidation phase of chemotherapy and 17 days prior to
admission had received week 4 (Dexamethasone, Vincristine, Doxorubicin) L-Asparaginase (weekly for 2doses) and daily 6-mercapto-

purine. He was admitted to the pediatric floor with febrile neutropenia with an Absolute Neutrophil Count (ANC) of 279. He was started on piperacillin/tazobactam and amikacin. He was clinically stable and there was no focus for his fever and his laboratory tests were normal except for a slight rise in both Alanine Transaminase (ALT) (172 I.U., normal range is 0–55), and Aspartate Transaminase (AST) (186 I.U., normal range 0–52), that was attributed to the chemotherapy received. Mucositis was noted on the day following admission and vancomycin was added. He continued to be febrile with worsening mucositis so amphotericin B was added empirically. A computed topographic scan of the chest and sinuses revealed no evidence of fungal infection. He re-

mained febrile for the next six days but was clinically improving. On hospital day 10, he developed tachycardia, respiratory distress and hypotension. Chest imaging revealed bilateral infiltrates. Liver function tests showed the following: ALT, 1280 I.U; AST, 4650 I.U; Total Serum Bilirubin (TSB), 3.2 mg/dl; direct bilirubin, 2.9 mg/dl; albumin, 2.2 gm/dl; Prothrombin time (PTT), 30 s; International Normalized Ratio (INR) 2.9 and Partial Thromboplastin Time (PTT), 180 s; and ammonia, 216 μg/ml. He was started on Vitamin K, actigal, meropenem, cryo-precipitate, and he was started empirically on N-acetyl cysteine. Over the next 12 hours, he developed multiorgan system failure with wor-

sening coagulation profile and metabolic acidosis. He then developed hypotension that was refractory to inotropes. His condition rapidly deteriorated and he eventually developed asystole and was not sal-

vageable by cardiopulmonary resuscitation. The family agreed to obtain a postmortem liver biopsy. Of note, hepatitis profile (Hepatitis A, B, and C serology) showed no evidence of recent infection; Cytomegalovirus (CMV) and Epstein–Barr virus (EBV) Polymerase chain reaction (PCR) were ordered and acetaminophen level was normal.

Liver biopsy

Microscopic examination of the liver biopsy showed sub-massive zonal necrosis affecting the peri-venular and mid zones of the liver. The portal tracts were largely preserved with minimal inflammation. The bile ducts, portal veins and hepatic arteries did not show any significant histologic changes. Diffuse macro-vascular steatosis was noted in the hepatocytes with no evidence of apoptosis. Many hepatocytes displayed nuclear smudging with chromatin margination and several cells were multinucleated. Two types of intra-nuclear inclusions were noted, acidophilic and basophilic (Fig. 1A). The inclusions were positive for multinucleated. Two types of intra-

nuclear inclusions were noted, nuclear smudging with chromatin margination and several cells were

marked fatty changes in the lower right corner. A bi-

patic parenchyma in the upper left corner and

section (20×) of the post mortem liver biopsy per-

Fig. 1. Post mortem diagnosis of HSV hepatitis in liver biopsy sections of case 1. A) A photomicrograph of a Hematoxylin and Eosin section (20×) of the post mortem liver biopsy performed in case 1. The biopsy reveals necrosis of hepatic parenchyma in the upper left corner and marked fatty changes in the lower right corner. A bi-

nucleated hepatocyte with intra-nuclear smudged inclusion is indicated by a red arrow. B) A photo-
micrograph (20×) of a liver biopsy section immu-

nostained for HSV 1 displays positive nuclear staining in one of the inclusion bodies indicated by a

red arrow.
demonstrated in case 2; in this case, early institution of acyclovir was life-saving. This favorable outcome matches the result reported by Navaneethan et al. [5]. However, in case 1, the patient did not receive acyclovir and diagnosis was only made post mortem.

In both cases above, the following symptoms were shared; fever, elevated transaminase levels and mucositis without clear cutaneous lesions. These findings are in agreement with Kaufmann et al. recommendations to consider HSV hepatitis in the differential diagnosis of immunocompromised patients exhibiting the above symptoms. The policy of our institution is based on the notion that only patients who are classified at high risk for developing fulminant Herpes hepatitis, in particular patients scheduled for a bone marrow transplant, receive anti-viral prophylaxis. If screening patients for HSV prior to intensive chemotherapy is to be carried out, IgM titers should be determined as elevation of this subtype indicates active infection. We cannot exclude that HSV hepatitis in the cases described above is “reactivation infection” in which IgG titers are already high. Due to the frequent delay in HSV diagnosis and the safety of acyclovir, we recommend empirically administering acyclovir in all febrile patients with mucositis suspected of HSV hepatitis and displaying high AST/ALT until it is excluded from the diagnosis. Although PCR results can be obtained in a few hours, nevertheless, this might prove few hours late as it was explicitly reported by Navaneethan et al. [5].

Conflict of interest statement

The authors declare no potential conflicts of interest. The patient guardian provided consent for images to be used for educational purposes.

Declaration of interest

None

Authorship statement

All authors declare that they have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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References

[1] Kaufman B, Gandhi SA, Louie E, et al. Herpes simplex virus hepatitis: case report and review. Clin Infect Dis 1997;24(3):334-6.
[2] Lakhan SE, Harle L. Fatal fulminant herpetic hepatitis secondary to tongue piercing in an immunocompetent adult: a case report. J Med Case Rep 2008;2:356. http://dx.doi.org/10.1186/1752-1947-2-356.
[3] Mortelé K, Bartoh M, Yacel K. Fulminant herpetic hepatitis in an immunocompetent pregnant woman: CT imaging features. Abdom Imaging 2004;29:682. http://dx.doi.org/10.1007/s00261-004-0199-y.
[4] Czartoski T, Liu C, Koelle DM, et al. Fulminant, acyclovir-resistant, herpes simplex virus type 2 hepatitis in an immunocompetent woman. J Clin Microbiol 2006;44(4):1584-6. http://dx.doi.org/10.1128/JCM.44.4.1584-1586.2006.
[5] Navaneethan U, Lancaster E, et al. Fulminant herpes simplex virus hepatitis – it’s high time we consider empiric treatment. J Gastroenterolin Liver Dis 2011;20(1):93-6.
[6] Norvell JP, Bley AT, Jovanovic BD, et al. Herpes simplex virus hepatitis: an analysis of the published literature and institutional cases. Liver Transpl 2007;13(10):1428-34.
[7] Pinna AD, Rakela J, Demetris AJ, et al. Five cases of fulminant hepatitis due to herpes simplex virus in adults. Dig Dis Sci 2002;47:750.
[8] Levitsky J, Duddempudi AT, Lakeman FD, et al. Detection and diagnosis of herpes simplex virus infection in adults with acute liver failure. Liver Transpl 2005;11(10):1498-504. http://dx.doi.org/10.1002/lt.21567.
[9] Wilder J, Chang S, Cardona D, et al. Acute liver failure in the setting of herpes simplex virus infection in a pregnancy case. J Clin Pathol 2015;68(2):89 - 92.
[10] Pasternak B, Hviid A. Use of acyclovir, valacyclovir, and famciclovir in the first trimester of pregnancy and the risk of birth defects. JAMA 2010;304(8):859-66.
[11] Spangler JR, Kirk JK, Knudson MP. Uses and safety of acyclovir in pregnancy. J Fam Pract 1994;38(2):186–92.
[12] Kang S-H, Chua-Gocheco A, Bozzo P, et al. Safety of antiviral medication for the treatment of herpes during pregnancy. Can Fam Phys 2011;57(4):427-8.