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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 immuonocomprimised 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

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admission had received week 4 (Dexamethasone, Vincristine, Doxorubicin) L-Asparginase (weekly for 2doses) and daily 6-mercepto 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 remained 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 (PT), 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, cryoprecipitate, and he was started empirically on *N*-acetyl cysteine. Over the next 12 hours, he developed multiorgan system failure with worsening 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 salvageable by cardiopulmonary resuscitation. The family agreed to obtain a post mortem 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-vesicular 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 the HSV type I specific immunostain (Fig. 1B), but were negative for the CMV specific immunostain.

The findings were suspicious of HSV hepatitis with sub-massive hepatic necrosis. Tissue sections were sent for the Pathology and Molecular Laboratory at Royal Victoria Hospital in Belfast, UK. Immunohistochemistry of the above sections confirmed the prior positive HSV immune staining performed at King Hussein Cancer Center (KHCC). Additionally, DNA was extracted from the tissue sections and we were able to detect the presence of HSV type I, but not type II, DNA by PCR. The presence of CMV DNA was also detected; however, no evidence of EBV DNA was detected.

Case 2

A 7-year-old male with a recent diagnosis of ALL (low risk, CNS 1) presented with oral mucositis and low grade fever 20 days after induction chemotherapy. The rest of his physical examination was normal and he had no evidence of organomegaly or any abdominal tenderness. Blood cultures were drawn and his laboratory tests revealed the following values: ANC, 264; ALT, 2430 I.U; AST, 2488 I.U; alkaline phosphatase, 256 I.U; TSB 1.6 mg/dL; Direct, 1.2 mg/dL. We thus admitted the patient and administered broad spectrum antibiotics. The patients' laboratory work revealed the following results: PTT, 39.7 s; PT, 18.5 s; INR, 1.56; D-dimer, 1.02 nmol/L; Fibrinogen, 309 mg/dl; Ammonia, 89 µmol/L. Viral work ups were also ordered including measuring IGM levels of HSV II, HCV, EBV, Hepatitis A virus (HAV) and CMV. Moreover, PCR tests for EBV, CMV and HSV type 1 were also ordered. Based on the above findings, intravenous gancyclovir and *N*-Acetyl cysteine infusion were started empirically. AST, 2488 I.U; alkaline phosphatase, 256 I.U; TSB 1.6 mg/dL; Direct, 1.2 mg/dL. We thus admitted the patient and administered broad spectrum antibiotics. The patients' laboratory work revealed the following results: PTT, 39.7 s; PT, 18.5 s; INR, 1.56; D-dimer, 1.02 nmol/L; Fibrinogen, 309 mg/dl; Ammonia, 89 µmol/L. Viral work ups were also ordered including measuring IGM levels of HSV II, HCV, EBV, Hepatitis A virus (HAV) and CMV. Moreover, PCR tests for EBV, CMV and HSV type 1 were also ordered. Based on the above findings, intravenous gancyclovir and *N*-Acetyl cysteine infusion were started empirically. HSV (type 1) PCR results obtained 48 hours after admission were positive and the patient was thus shifted to IV acyclovir. The follow up examination of liver enzyme levels showed a significant improvement until they became within the normal reference range 60 hours after the initiation of acyclovir treatment (Fig. 2). The patient was later discharged after 7 days of hospitalization without any complications and was started on oral acyclovir for an additional week and the patient did not report back to the hospital.

Discussion

HSV hepatitis is an aggressive disease of high mortality (> 80%) if left untreated [1,6]. Patient symptoms include fever (82%), anorexia with nausea and/or vomiting (18%), abdominal pain (33%), leukopenia (43%), and coagulopathy (20%) [1]. Additionally, the disease may spread outside the liver [8]. Characteristic oral and/or genital lesions are often missing [1], In this case diagnosis is made only through a trans-jugular liver biopsy, revealing intranuclear inclusions and HSV antigens, and/or the detection of viremia [9,10].

Treatment of HSV infections with acyclovir was not in clinical use until its introduction in 1983. Therefore, information on its efficiency and safety in treating HSV hepatitis was not available [1]. Since then, however, it proved to be a safe and effective therapy for HSV infections [11–13]. The empirical use of acyclovir in suspected HSV hepatitis is

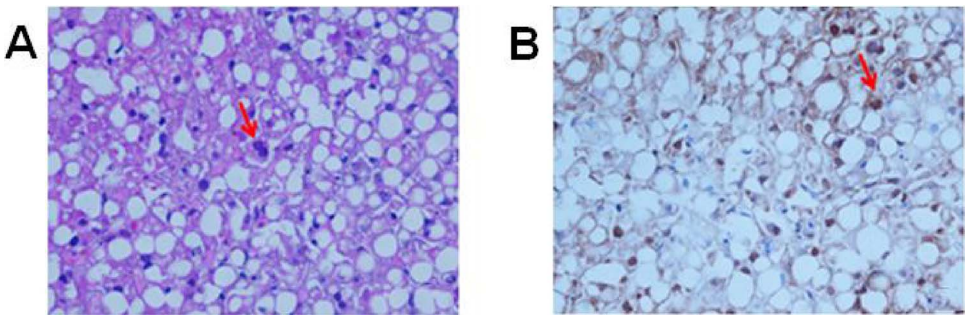

Fig. 1. Post mortem diagnosis of HSV hepatitis in liver biopsy sections of case 1.
A) A photomicrograph of a Hematoxylin and Eosin section (20×) of the post mortem liver biopsy performed in case 1. The biopsy reveals necrosis of hepatic parenchyma in the upper left corner and marked fatty changes in the lower right corner. A binucleated hepatocyte with intra-nuclear smudged inclusion is indicated by a red arrow. B) A photomicrograph (20×) of a liver biopsy section immunostained for HSV 1 displays positive nuclear staining in one of the inclusion bodies indicated by a red arrow.

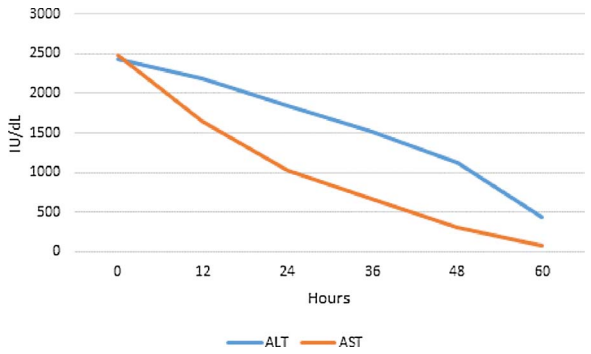

Fig. 2. Change of Serum levels of ALT and AST enzymes after the initiation of empirical acyclovir treatment in case 2. Serum samples were withdrawn at the indicated time points from the patient described in case 2 following the initiation of acyclovir treatment (Time of initiation = Zero). ALT and AST levels are expressed in International Units (I.U) while time is expressed in hours.

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 immuonocomprimised 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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