Case Report

Hemophagocytic syndrome

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ABSTRACT

This case report is about an elderly man who presented with a long-standing history of high-grade fever and weight loss. He initially had only hepatosplenomegaly, but then developed jaundice. He also had pancytopenia and raised liver enzymes. His septic screen was negative, but he had a positive Monospot test and immunoglobulin G for Epstein-Barr virus. The liver biopsy showed sinusoidal phagocytosis and the subsequent bone marrow aspiration and biopsy showed significant hemophagocytosis, hence Hemophagocytic syndrome was diagnosed. The fever was refractory to antibiotic and anti-tuberculosis therapy, but it responded only partially to steroids. Full response was only noticed following anti-viral treatment in the form of intravenous Ganciclovir. The patient's general condition, liver enzymes, bilirubin, hematological parameters and even the weight returned back to their normal range 2 weeks after Ganciclovir therapy. Cessation of this drug resulted in relapse of his symptoms and oral antivirals did not help. Splenectomy, steroid pulse therapy and immunosuppressive treatment were only partially helpful. Reintroduction of Ganciclovir did help for a short period. We conclude that our patient had virus-associated hemophagocytic syndrome most likely related to Epstein-Barr virus infection, which was then confirmed by the splenic biopsy, and that Ganciclovir can be of great help in eradicating the virus and treating the disease, provided that it is given for a long enough period.

Keywords: Histiocytosis, Epstein-Barr virus, steroids, antiviral drugs.

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Hemophagocytic syndrome, which is also called Histiocytosis, is associated with exaggerated activity and proliferation of macrophages or histiocytes.[1] Many infections can induce this disease including viruses. In 1979, Risdall et al was the first to describe the disease, virus-associated hemophagocytic syndrome (VAHS).[2] Different viruses can be responsible, but Epstein-Barr virus (EBV) is the leading cause among them, especially in children.[3] The liver, as many other organs in the body including the spleen, lymph nodes,[4-6] and even the retina,[7] can be influenced by a significant degree of hemophagocytosis. So far, little has been reported about the treatment of this disease, and all therapeutic regimens used are still not very satisfactory. Steroids, immunosuppressive, and anti-viral drugs were tried,[8] but the mortality is still high, especially in EBV-associated hemophagocytic syndrome.[3] Splenectomy can be of help in some studies. In this case report, we will discuss the usefulness of anti-viral treatment compared to other modes of therapy in this patient.

Case Report. A 68-year-old man presented with a 3-month history of high-grade fever, which was mostly at night and associated with chills and night sweating. In addition, the patient had anorexia and lost around 10-15 Kg of his weight over the same period. He also had long-standing, but mild epigastric pain with no associated gastrointestinal symptoms. Two years ago, he was treated for brucellosis. Physical examination on admission showed a temperature of 39^0C and mild hepatosplenomegaly. The patient's preliminary investigations showed slight leukopenia and

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thrombocytopenia, in addition to a high alkaline phosphatase and alkaline transaminase. Full septic screen was negative, including sputum for bacteria and acid fast bacilli, Mantoux test, Brucella serology and culture, Malarial screen, Hepatitis B and C serology, complement fixation tests for Influenza A and B, Adenoviruses, Chlamydia, and Mycoplasma in addition to serology of Herpes and Cytomegalo virus (CMV). Schistosoma titer was high and the patient received the proper treatment for that. The only significant tests were a positive immunoglobulin G (IgG) serology for EBV and a positive Monospot test. The autoimmune screen and tumor markers were negative. The initial radiological investigations including computerized tomography (CT) of chest, abdomen and brain were normal. Bone scan was also normal. The initial bone marrow (BM) biopsy was normal. Esophageal and gastric biopsies were negative for malignant cells. The patient was started, from admission, on different courses of strong intravenous antibiotics, including treatment for Brucellosis but with no improvement. A trial of anti-tuberculosis for a month was made but still with no benefits. Steroids helped initially to relieve the fever but only for few days and then the fever relapsed, Figure 1. In fact, the patient continued to deteriorate both clinically and biochemically. In addition, the patient developed hyperbilirubinemia, sever pancytopenia (Figure 2) pulmonary infiltrates, ascites and massive hepatosplenomegaly. Laparoscopy was eventually carried out, which showed multiple whitish nodules over the liver surface. The liver biopsy (Figure 3), showed chronic hepatitis with sinusoidal erythrophagocytosis, which can be related to viral infection. So, the diagnosis of Hemophagocytic syndrome was made, and to confirm it a repeated BM aspiration and biopsy was carried out, almost one month following the initial one, and showed significant hemophagocytosis. Fundoscopy also showed retinal soft exudates, which are probably related to hemophagocytic syndrome. As the disease is very likely to be virus-induced and as the steroids were not very helpful in this patient, a trial of antiviral therapy was made in the form of intravenous Ganciclovir. The patient became afebrile after the 3rd dose of Ganciclovir and he showed dramatic improvement both clinically and biochemically (Figures 1 and 2). His liver enzymes, bilirubin, and hematological parameters became normal in 2-3 weeks time. He also gained weight. Ganciclovir therapy was continued for 4 weeks, and oral Valaciclovir was commenced with the tapering doses of steroids. A few days later however, the same pattern of fever recurred. Methyl Prednisolone in pulse doses was started, followed by oral steroids, which helped only for few days (Figure 1). Splenectomy was then considered, but the patient refused, so, Ganciclovir was restarted and the fever

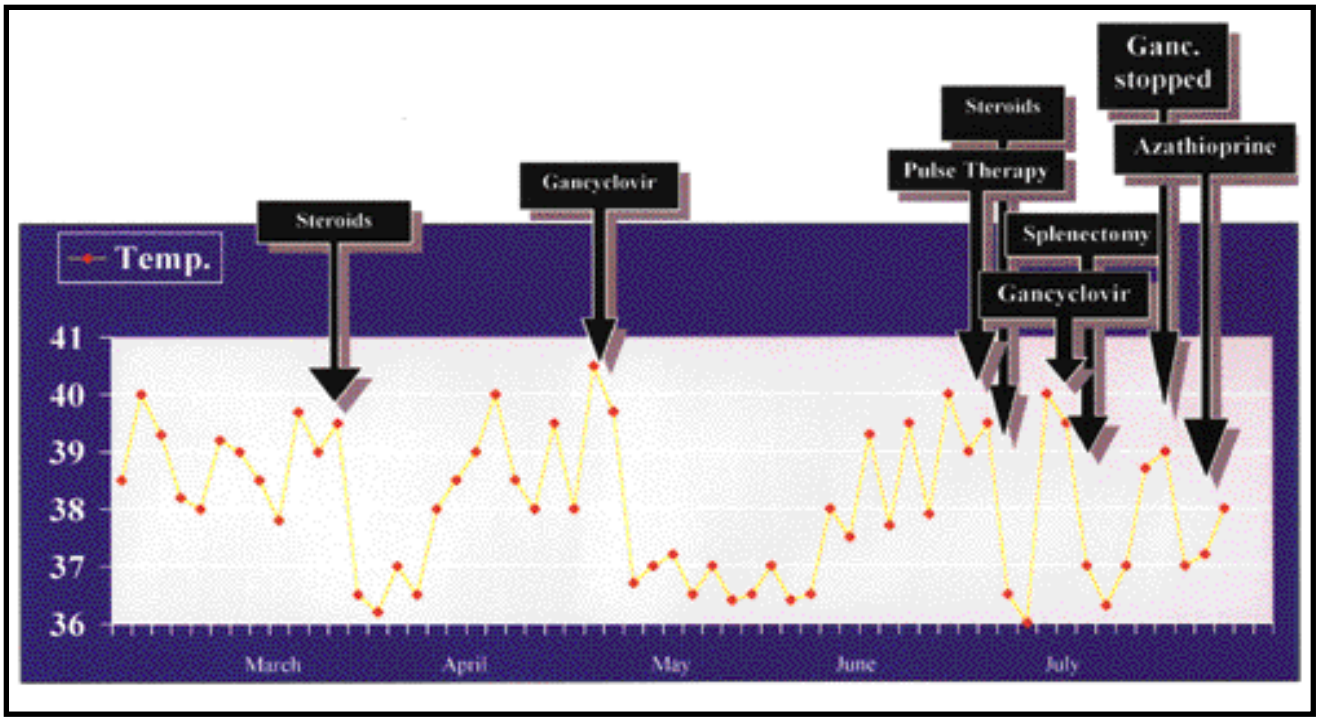

Figure 1 - The temperature plotted randomly once every 3 days.

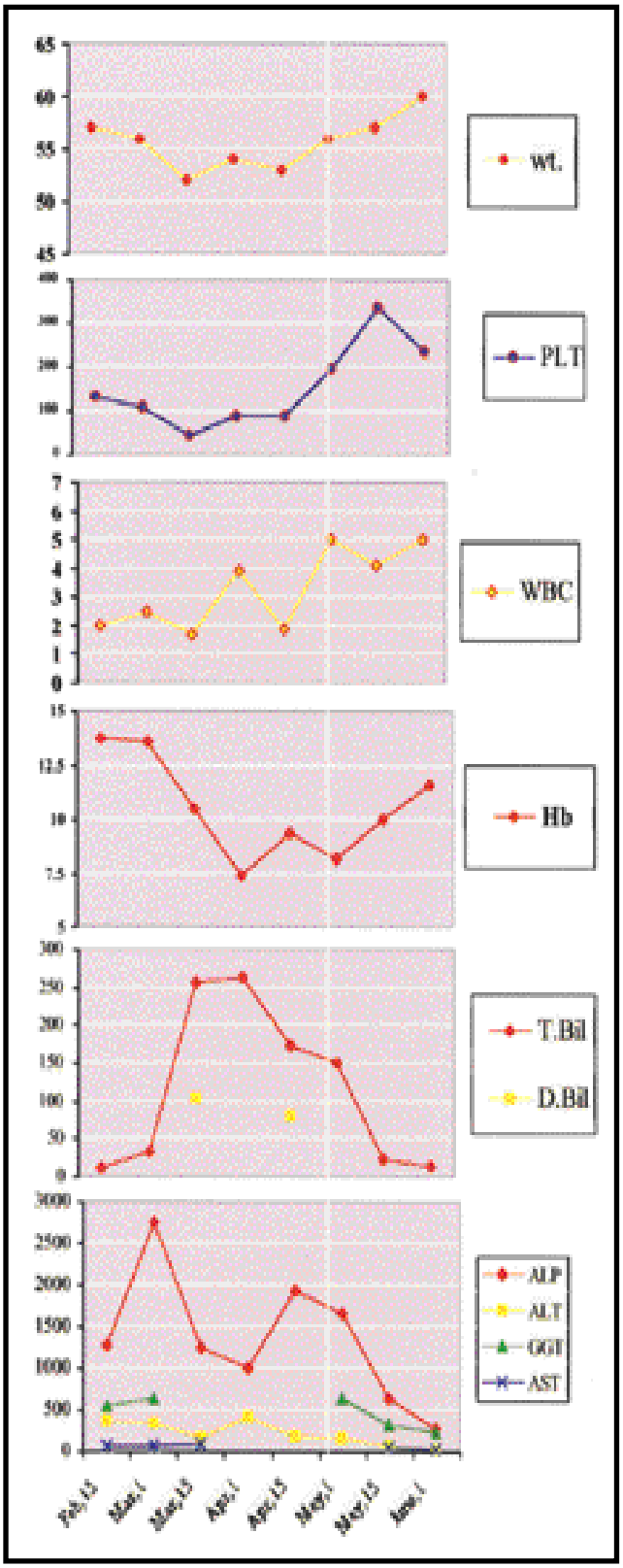

Figure 2 - This figure shows the change in the patient's weight, biochemical and hematological data from admission until Ganciclovir was started, which is indicated in the graph by the white line.

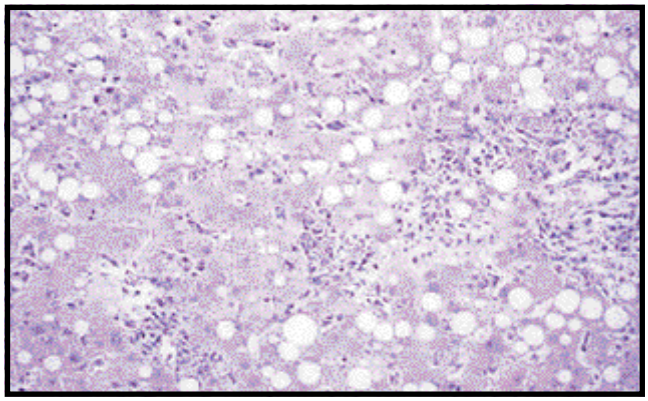

Figure 3 - (a) Liver biopsy, showing sinusoidal erythrophagaocytosis (H&E stain).

subsided. Three days later, the patient consented for splenectomy, and the spleen was removed for both diagnostic and therapeutic purposes (Figure 1). The spleen was grossly enlarged and it showed, microscopically, again significant hemophagocytosis possibly related to EBV (incyto-hyperdisation). The patient remained afebrile for almost 10 days, but the fever recurred again in spite of Ganciclovir therapy. Ganciclovir was stopped and immunosuppressive treatment in the form of Azatheoprine was started. The temperature improved but did not subside completely (Figure 1). The patient then requested to leave the hospital against medical advice, and was discharged on Azatheoprine and was asked to come to the clinic after a week, but he did not show up. Three months later, we were informed that he was admitted to a regional hospital with acute intestinal obstruction. He was operated upon immediately, but they could not save him. No biopsy was taken, and so, the cause of his intestinal obstruction and ultimately the cause of his death remains obscure.

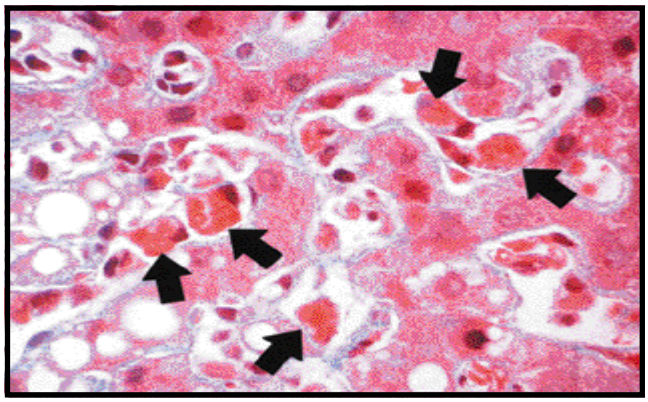

Figure 3 - (b) Arrows are pointing out multiple phagocytes inside the liver sinusoids within which are several red blood cells - characteristic of hemophagocytic syndrome (Trichrome stain).

Discussion. Hemophagocytic syndrome is classified broadly into malignant and reactive,[9] and once reactive hemophagocytic syndrome is diagnosed, a great effort has to be spent to find out what caused it so as to try to treat it. Infections are commonly responsible, as are some tumors and diseases. Viruses including, EBV,[10,11] cytomegalovirus,[12] adenovirus, herpes simplex and varicella zoster viruses are the most important. Other organisms like enteric bacteria, mycobacteria,[13] Brucella,[14] leishmania,[15] and Babesia[16] can also be responsible. In the case we are presenting, the fever, pancytopenia and liver dysfunction were caused by hemophagocytic syndrome as proved by liver, BM and lately splenic biopsies. As the screening for tumors and infections that can induce the disease were negative, except for a positive IgG for EBV, which does not necessarily indicate an acute infection, unlike IgM, and a positive Monospot test, EBV was suspected to be responsible for the patient's disease. That was then confirmed by the splenic biopsy. Steroid therapy, Methylprednisolone pulse therapy, is reported to be of help in these cases,[8] but, unfortunately it did not help much in our case. The supportive measures and intravenous antibiotics did not help as well. On this basis, other measures should be considered especially if we know that this patient carry a poor prognosis. Generally, the poor prognostic features include, age more than 30 years, presence of anemia, thrombocytopenia, jaundice, disseminated intravascular coagulation, increased ferritine, and increased ß$_2$-microglobulin,[9] and most of these fit our patient. As there is strong evidence of EBV infection causing the patient's disease, and as the patient has multiple poor prognostic signs, any possible means available should be tried, including antiviral therapy. Antiviral drugs were tried, in some reports, but not much data about the outcome is available in this field.[3] We, however, tried Ganciclovir, an antiviral drug similar to aciclovir structurally which was chosen because it is very strong and effective against CMV as well as EBV, and the patient improved from all aspects. However, he relapsed shortly after stopping Ganciclovir, assuming that he had had a long enough course of 4 weeks. Reintroduction of Ganciclovir showed full response again, but this time the patient relapsed while on this drug, which raises the possibility of the development of resistance. Splenectomy was not very helpful in our case. Finally, immunosuppressive treatment, which we tried at the end, was reported to be of help in such cases,[3] but we could not fully assess the patient's response to this as the patient was lost to follow up shortly after it had been started.

In short, the patient had proven EBV-induced hemophagocytic syndrome tried on all possible modes of therapy, of which antiviral therapy showed a better response compared to the other modes of therapy.

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