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Brief communication (Original)

Surviving acquired severe nonmalignant hemophagocytic syndrome

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Background: Hemophagocytic syndrome (HPCS) is not rare in Thailand. At present the outcome in severe cases is often unsatisfactory because of a delay in diagnosis and improper management. From 1999 to 2011, the authors have gained experience in the management of severe acquired nonmalignant HPCS in Thai adult patients. From 1999 to 2003, three out of 10 patients died. During 2005–2011, seven patients with severe HPCS survived. This improvement stimulated the authors to analyze clinical manifestations, etiology, and management of these patients.

Objective: To find the keys to successful outcomes in the management of acquired severe nonmalignant HPCS in seven survivors during 2005–2011. To alert physicians that acquired severe nonmalignant HPCS may be cured.

Materials and Methods: The records of ten patients with HPCS were analyzed. Between 1999 and 2003 three patients died. Between 2005 and 2011 seven patients survived.

Results: The three patients during 1991-2003 may well have died because of delayed diagnosis and improper management. One case of HPCS was diagnosed after death. In the other two cases etiologies were not readily identified and dealt with. In the surviving group, treatment was started as soon as HPCS was suspected or diagnosed. This consisted of removal of any known cause and aggressive management of associated conditions and complications.

Conclusion: Adults who acquire severe nonmalignant HPCS can be treated successfully. The key roles for this success are early diagnosis and appropriate management. The best supportive care and close observation by the team of hematologists and physicians also determines patient survival.

Keywords: Therapy, acquired severe nonmalignant hemophagocytic syndrome

Acquired hemophagocytic syndrome (HPCS) or acquired hemophagocytic lymphohistiocytosis (HLH) was first reported by Chandra et al. in 1975 to have very high mortality rates of around 70% [1]. The classical features of HPCS consist of fever for 1–2 weeks, hepatosplenomegaly and lymphadenopathy accompanied by progressive cytopenia, multiorgan failure of liver, brain, lungs, kidneys, heart, and disseminated intravascular coagulation (DIC) and ischemia severe bleeding and death [2]. Marked increase of serum ferritin and lactic acid dehydrogenase were almost always found in severe cases. Hyperferritinemia indicates a poor prognosis [3] and hypertriglyceridemia was uncommon [4]. Etiologies of acquired HPCS were divided into two groups: nonmalignant and malignant lymphoma associated HPCS. This division was reported 40–60% in Asian populations [2, 5, 6]. Malignant lymphoma was found less frequently in Caucasians [7]. The etiologies of nonmalignant HPCS consist of various noninfectious and infectious disorders. Ebstein–Barr virus (EBV) was first reported as a cause of HPCS in 1979 by Risdall [8] followed by Sullivan in 1995 [9] and Wong in 1996 [10]. EBV caused high fatalities and also played a role in the pathogenesis of malignant lymphoma associated with HPCS [11-14]. Recently, dengue hemorrhagic fever has also been reported as a precipitating cause of HPCS [15] and it may induce death in severe cases [16]. Other microorganisms that may be responsible for HPCS include cytomegalovirus (CMV), Coxsackie virus, rubella, hepatitis C, Gram negative bacterial infections such as from pseudomonas, *Klebsiella*, and disseminated tuberculosis, protozoal, and fungal infections [17]. Autoimmune diseases such as systemic lupus erythematosus (SLE) [18] and adult Still's disease [19],

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as well as drugs and toxins from the raw liver of monkfish have also been blamed [20].

The pathogenesis of HPCS [21-25] represents an immune dysfunction in the host. Macrophages became hyperactive following antigen stimulation. In combination with increased apoptosis, caused by activation of the Fas ligand gene, the macrophages increase hemophagocytosis resulting in severe cytopenia. T lymphocytes are also stimulated by the macrophages. In the presence of T- and NK-cell dysfunction, the ineffective hyperimmune response leads to massive release of many cytokines including tumor necrosis factor a (TNF-α), interleukins (ILs) including IL1, IL6, IL12, and IL18, interferon γ, and other mediators. These substances injure the endothelial cells of small vessels, causing a leakage syndrome and release of tissue factors leading to hypercoagulability DIC, shock, and multiorgan failure. EBV plays an important role in inducing more severe intractable HPCS. EBV stimulates the TNF-α gene causing increase of TNF-α in the circulation [26]. Furthermore, EBV causes uncontrolled proliferation of infected T cells, leading to a T-cell malignant lymphoma that resists treatment [26]. TNF-α also causes hypoalbuminemia [27]. Better understanding of the pathogenesis of HPCS has been associated with more effective treatment [28]. This also includes prompt removal of any known or suspected etiology, the use of immunomodulators, pulse methyl prednisolone (MP), intravenous immunoglobulin G (IV IgG) and immunochemotherapy, such as cyclosporin A and etoposide [29-32]. Adjunctive plasma exchange is conducted to remove cytokines, toxins and thromboplastic substances [33, 34]. In cases of EBV infection, IV anti-EBV therapy is associated with better outcomes [32, 35, 36]. During 1999–2011, the authors managed ten acquired severe nonmalignant HPCS. Three patients seen during the earlier period (1999–2003) died. Patients seen during the years 2005–2011 survived with complete recovery. The different outcomes from these two groups of patients stimulated the authors to retrospectively analyze their etiologies, clinical manifestations, and management.

Materials and method

Patients were classified according to the time of their admission. The first period between 1999 and 2003 consisted of three fatal cases in two men and one woman aged 31–77 years (mean 59 ± 20). During 2005–2011 there were seven patients, three men and four women, aged 26–84 years (mean 50 ± 30) who all survived. This retrospective medical record study was approved by the Ethics Committee of Vichaiyut Hospital and Medical Center.

The patient's records were retrospectively studied. Laboratory investigations included complete blood count (CBCs), blood chemistry including blood urea nitrogen (BUN), creatine (Cr), serum alanine aminotransferase (SGPT), serum aspartate aminotransferase (SGOT), γ-glutamyltransferase (GGT), albumin, electrolytes, lipids, serum ferritin, and lactate dehydrogenase (LDH), and chest X-ray images, and urine and stool analysis. Investigation for possible etiologic agents included hemoculture, serology for EBV, CMV, hepatitis B and C viruses, Coxsackie and rubella viruses, and serology for autoimmune diseases were performed in all subjects. Bone marrow was examined in every case to demonstrate hemophagocytosis, to search for infectious agents, and exclude malignancy. Diagnosis of HPCS was based on one the following criteria: fever, progressive cytopenia, multiorgan failure, hemophagocytosis, and hyperferritinemia. A disseminated intravascular coagulopathy (DIC) diagnosis was based on clinical evidence of ischemia or bleeding, along with thrombocytopenia, prolonged partial thromboplastin time, prothrombin time and thrombin time, and increased D-dimer of more than four times the normal value. The diagnosis of EBV disease was based on the demonstration of EBV RNA in the bone marrow or lymph nodes or by demonstration of an increased EB viral load of more than one million copies/ml by PCR or by IgM antibody immunoreactivity.

Treatment

Therapy was started immediately after diagnoses and consisted of removal of any recognized etiological factors where possible as well as circulatory support. Intravenous anti Epstein Barr Virus (EBV) therapy was started in cases of confirmed EBV infection. Pulse methyl prednisolone (MP) 1 g intravenously for 3-5 days along with IVIgG 1 gm/kg/day for 2 days were started. Plasma exchange (2.5 times of the plasma volume) was performed using the following criteria: failure to respond to pulse MP and IVIgG, total bilirubin more than 10 mg% or acute DIC with massive bleeding and failure of blood component therapy. One unit of platelet concentration was given after plasma exchange. Hemodialysis was performed in case of oliguric renal failure. Patients were closely followed by a team of hematologists and intensivists.

Results

Table 1 shows clinical and laboratory data as well as treatment and outcomes. Of the three fatal cases, all had severe pancytopenia, and two had DIC and multiorgan failure [2]. Patient 1 died before HPCS was diagnosed. Patient 2 had septicemia caused by *Klebsiella* liver abscess and presented with acute respiratory distress syndrome (ARDS), severe hepatitis, and renal failure. She received the full treatment protocol for HPCS, but did not improve, partly because of failure to evacuate the liver abscess. Patient 3 received MP, IV IgG, and VP16, but did not improve, losing consciousness, developed ARDS, renal failure, and deep jaundice. EBV was diagnosed 12 hours prior to death. IV anti-EBV therapy and plasma exchange were performed without success [14].

Patient 4 presented with severe hepatitis, deep jaundice, semiconsciousness, renal failure, hyperferritinemia, and high serum LDH. Pulse (MP) IV IgG, and VP-16 therapy were administered without improvement. Plasma exchange was performed for 7 days along with hemodialysis. PCR for EBV was positive after the plasma exchange. Intravenous ganciclovir was given along with supportive measures. The patient survived.

Patient 5 presented with high fever and tonsillar patches. She was treated for infectious mononucleosis including administration of oral anti-EBV. Seven days later, she developed progressive cytopenia and hemophagocytosis in the bone marrow, massive generalized lymphadenopathy including mediastinal and para-aortic lymph nodes, followed by ARDS. She received pulse MP, IV IgG, and intravenous acyclovir. She recovered from HPCS [36].

Patient 7 developed severe HPCS following consumption of raw monkfish liver. Multiorgan failure included CNS dysfunction, renal failure, cardiopulmonary distress, hepatitis, hyperbilirubinemia, high serum ferritin, and LDH. Pulse MP and IV IgG were given without success. Plasma exchange was performed for 7 days. There was some improvement, but the fever persisted. A second course of IV IgG and pulse MP were given and the fever subsided. However, he developed DIC, which was successfully treated by heparinization. He recovered completely [20].

Patient 8. This 36-year-old woman had known refractory systemic lupus erythematosus (SLE) and was taking herbal medications before she developed HPCS with multiorgan failure: severe hepatitis, semiconscious, renal failure, and hyperbilirubinemia. The patient received pulse MP and IV IgG, along with hemodialysis. She remained in hospital for 20 days and recovered from HPCS.

Patient 9. A 26-year-old woman with adult Still's disease developed HPCS with multiorgan failure became semiconscious and developed acute respiratory distress syndrome, hepatitis, jaundice, very high serum ferritin, and progressive anemia. She received pulse MP and IV IgG for 2 courses with cyclophosphamide. She recovered from HPCS.

Patient 10. A 38 year-old man with untreated chronic active hepatitis B. His hepatitis progressed to acute fulminant hepatitis B. HPCS developed following onset of fulminant hepatitis B. He presented with severe anemia, thrombocytopenia, severe DIC with massive gastrointestinal bleeding, semiconsciousness and lung involvement associated with very high serum ferritin. Pulse MP and a limited amount of IV IgG were given after the first plasma exchange for treatment of severe DIC and bleeding. After the completion of plasma exchange, IV IgG was given at a standard dose. Despite the administration of pulse MP + IV IgG, the patient developed severe encephalopathy and ARDS. Plasma exchange was again performed, and the patient completely recovered from HPCS. He was then started on oral tenofovir after recovery.

Discussion

Adult acquired severe nonmalignant HPCS can be treated successfully with complete recovery. After 2005, our seven patients with severe HPCS survived with complete recovery. Success depended on rapid diagnosis and prompt appropriate management. Intravenous anti-EBV therapy appeared very helpful in 2 cases. Extensive literature shows that mortality rates associated with HPCS and EBV infection are high [37-39]. However, there are reports showing successful treatment of HPCS associated with intravenous anti-EBV therapy [41-43]. We did not use immunochemotherapy except in the case of the adult Still's disease because we felt that this treatment may suppress the immune response to concurrent infection. Perhaps the most important factor for survival is close cooperation between hematologists and intensivists in caring for such fragile patients.

Table 1. Clinical and laboratory manifestations, treatment, and outcome of acquired nonmalignant hemophagocytic syndrome in ten Thai adult patients

Patient no (Year)	Sex Age	*Etiology*	Cytopenia			Organ failure and related laboratory abnormality										Treatment	Out come
			RBC	WBC	Platelets	DIC	CNS	RF	Lung	Heart	Splenomegaly	Hepatomegaly	SGPT	TB	SF	LDH		
1 [2] (1999)	M 75	Pseudomonas Septicemia	++	++	++	NF	NF	++	+	NF	NF	+	+	++	ND	ND	*Antibiotic*	dead
2 [2] (2003)	F 72	Klebsiella Septicemia and liver abscess	++	++	++	+	NF	+	++	NF	NF	+	++	+	ND	ND	Antibiotic MP, IVIgG VP-16, PEx	dead
3 [15] (2002)	M 31	Acute EBV PCR >14 mil/cp/ml (found 6 h. before – death)	++	++	++	+	+	+	++	NF	+	+	+	++	NF	++	MP, IVIgG VP-16 Acyclovia, PEx	dead
4 (2005)	M 77	Acute EBV PCR + in blood (after PEx)	++	NF	++	+	++	++	NF	NF	NF	NF	++	++	+++	++	VP-16, PEx x 7 d. gancyclovia v	survived
5 [37] (2011)	F 84	Acute EBV EBER + in LN	+	+	+	+	NF	NF	++	NF	+	LN ++++	NF	NF	NF	NF	Acyclovia v MP,IVIgG	survived
6 [16] (2008)	F 46	Dengue hemorrhagic fever type 2	++	NF	++	+	+	NF	+	++	+	NF	++	NF	++	++	MP, IVIgG	survived
7 [21] (2009)	M 38	Toxin from raw monkfish liver. Thymoma	+	NF	++	+	++	++	++	+	+	NF	+	++	++	+	MP, IVIgG PEx 20 U/d/x7 d 2nd MP, IVIgG HDx 10 days	survived
8 (2010)	F 36	SLE – relapse + Herp Medicine	+	+	+	NF	++	++	NF	NF	NF	NF	++	++	ND	ND	MP, IVIgG Hemodialysis	survived
9 (2011)	F 26	Adult Still's disease	+	+	+	NF	+	NF	+	NF	NF	NF	+	+	++++	ND	MP, IVIgG Cyclophosphamide	survived
10 (2011)	M 38	Fulminant hepatitis B	++	NF	++	++ massive GI bleeding	++	+	++	NF	NF	NF	++	+	++++	ND	PEx 20 U/d x 2 IVIG, MP Rx virus B	survived

EBV = Ebstein–Barr virus, SLE = Systemic lupus erythematosus, GI = gastrointestinal. Cytopenia: RBC Hct <30% (+), <24% (++). Wbc <4000 (+), <2000 (++); platelets <100,000 (+), <50,000 (++). DIC = disseminated intravascular coagulation: no bleeding (+), bleeding (++). CNS: lethality, delirium (+), severe mental changes (++). RF = renal failure: azothermia (+), required hemodialysis (++). Lung: dyspnea (+), required respirator (++). Heart: cardiomegaly (+), congestive heart failure (++). TB = total bilirubin: >2 mg% (+), >10 mg% (++), SGOT >200 (+), >2000 (++). SF = serum ferritin >1000 (+), >5000 (++), >10,000 (+++), >100,000 (++++). LDH >1000 (+), >2000 (++). MP = methyl prednisolone. IV IgG = intravenous immunoglobulin G. PEx = plasma exchange. NF = not found.

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