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Case Report

A case of combined immunodeficiency with predominant T cell defect accompanied with severe cytomegalovirus infection

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Abstract

We describe a fulminant infant case of hemophagocytic syndrome (HPS) which might have been associated with cytomegalovirus (CMV) infection. After his admission, pancytopenia and liver dysfunction became severe requiring bone marrow examination and liver biopsy. Bone marrow examination showed much erythrophagocytosis. A liver needle biopsy revealed many CMV inclusion bodies. The IgM antibody against CMV was positive in his serum. His lymphocyte surface marker analysis revealed a marked decrease in T lymphocyte percentage (0.8%). We supposed that he had combined immunodeficiency with predominant T cell defect. He suddenly died due to heart failure despite various therapies having been performed including antiviral drugs (Gancyclovir and Foscarnet), during work up for bone marrow transplantation. CMV infection in children with combined immunodeficiency disorders has high morbidity and mortality. Development of effective therapy to CMV infection is essential for treatment of severe immunodeficiency syndrome.

Introduction

The hemophagocytic syndromes (HPS) are rare and lethal disorders characterized by several clinical features including fever, organomegaly, pancytopenia and hyperferritinemia[1)]. We describe an infant with combined immunodeficiency and predominant T cell defect, who suffered systemic infection with cytomegalovirus (CMV) including encephalitis, pneumonia and HPS. The clinical symptoms were progressive and intractable despite exchange transfusion therapy, CMV-high-titer γ globulin, steroid pulse therapy and antiviral therapy.

Case Report

The 2-month-old male infant had developed persistent high fever (>38.5°C) and anorexia for one week, and was referred to our institute. He was vaginally delivered at 39 weeks gestation with a birth weight of 3,452 g. He was a breast-fed child and developed well until the onset of symptoms. Other family members had been well, including his 2 sisters and 1 brother.

His physical examination revealed him to be pale, with a temperature of 39.2°C, 170 per minute pulse and a respiratory rate of 30 per minute. The liver was enlarged 5 cm below the right costal margin and the spleen 3 cm below the left costal margin. No rash or

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Table 1 Laboratory findings

WBC	6,900/ul	TP	4.9 g/dl	CMV-IgM	3.70
Neut	60.8%	T-bil	0.94 mg/dl	C7-antigenemia	100/26000
Lymph	31.8%	D-bil	0.53 mg/dl	EBV VCA-IgM	<10
Mono	6.8%	BUN	12.3 mg/dl	EBV EBNA	10
RBC	343×10^4/ul	Cr	0.32 mg/dl	EBV VCA-IgG	10
Hb	9.7 g/dl	UA	2.4 mg/dl	HSV IgM	(−)
AST	1,278 IU/L	Glu	114 mg/dl	HIV	(−)
ALT	445 IU/L	Na	141 mEq/l		
LDH	2,368 IU/L	K	4.9 mEq/l		
ALP	638 U/L	Cl	115 mEq/l	Urine	
LAP	202 IU/L	Ca	7.2 mg/dl	Protein	(−)
γ-GTP	270 U/L	CRP	1.8 mg/dl	Blood	(−)
				Glucose	(−)
		IgG	323 mg/dl	RBC	1/5-10/F
		IgA	7.09 mg/dl	WBC	20〜30/1F
		IgM	49.1 mg/dl	β-2MG	1,027 μg/l
CD3	0.8%	Ferritin	>10,000 ng/ml		
CD4	0.5%	s-IL2	4,060 U/ml		
CD8	0.3%	ADA	39.3 IU/l		
CD19	86.4%	CON-A blastogenesis	1002 CPM		
CD16	5.3%	PHA blastogenesis	418 CPM		
CD20	85.5%				
HLA-DR	83%				
NK-cell activity	11%				

adenopathy was noted. His laboratory findings showed pancytopenia, liver dysfunction and hyperferritinemia (Table 1). After admission, his pancytopenia and liver dysfunction became severe, requiring bone marrow examination and liver biopsy (day 11). Bone marrow examination showed much erythrophagocytosis. The IgM antibody against CMV was positive. A liver needle biopsy revealed CMV inclusion bodies (Fig. 1). Epstein-Barr virus (EBV) indirect fluorescent antibodies against viral capsid antigen (VCA) IgM and early antigen (EA) IgG were negative. We made a diagnosis of CMV-associated hemophagocytic syndrome (HPS). His chest X-ray and computed tomography (CT) showed no thymus-like components. Lymphocyte surface marker analysis revealed a marked decrease in the percentage of T lymphocytes (0.8%). The phytohemagglutinin (PHA) and concanavalin A (ConA) blastogenesis decreased. Serum immunoglobulin levels were normal. Since he did not have congenital heart disease, hypocalcemia or the characteristic facial features of Di George syndrome, combined immunodeficiency with predominant T cell defect was diagnosed.

Severe pancytopenia required exchange transfusions and CMV-high-titer γ-globulin and steroid pulse therapy. CMV antigenemia was markedly high, consequently antiviral drug treatment (Gancyclovir and Foscarnet) was initiated. The dosage of Gancyclovir was 5 mg/kg per dose twice a day and the dosage of Foscarnet was 60 mg/kg per dose three times a day. The response to therapy is shown in Fig. 2. After three weeks his level of consciousness deteriorated. Cerebrospinal fluid (CSF) examination revealed 15 mg/dl protein and normal lymphocytes. Brain CT findings showed no edema or atrophy. CSF was not cultured for CMV. Although we used two antiviral drug treatments, the amount of CMV antigenemia did not decrease and his level of consciousness remained unchanged. At the same time that his level of consciousness deteriorated,

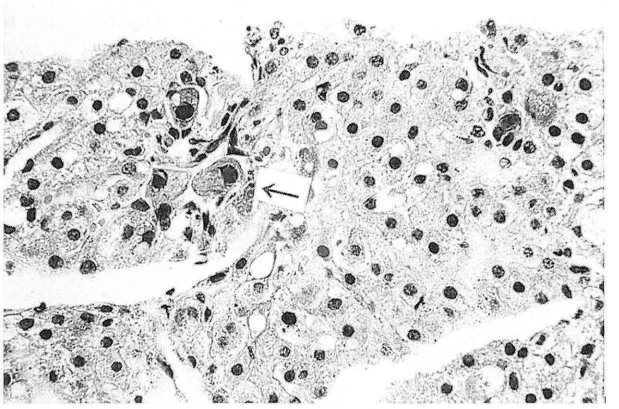
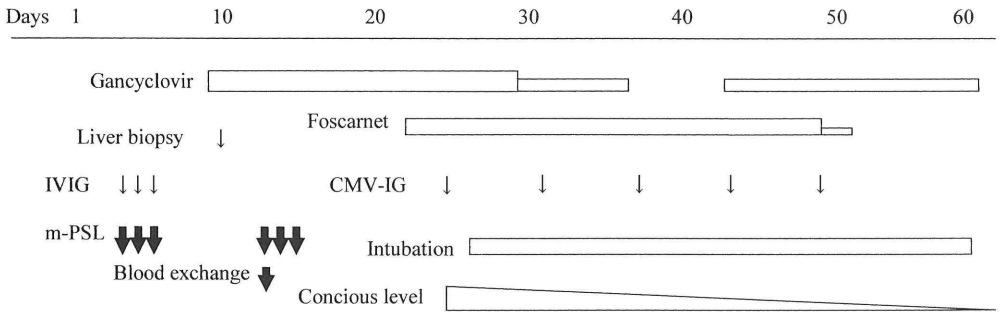


Fig. 1 There were many inclusion bodies (arrows) in liver tissue. (Hematoxylin-eosin staining, ×200)



WBC	6900	2300	700	2200	3700	2800	2900	2600
Hb	9.7	9.6	7.8	9.4	9.5	8.3	8.2	8.5
Plt	17.8	9.6	7.1	15.9	16.5	47.6	39.9	40.7
ALT	1278	124		608	165	124	97	50
AST	445	93		117	67	75	55	50
LDH	2368	1067		1373	1011	587	545	488
CRP	1.8	0.5		<0.3	<0.3	<0.3	<0.3	<0.3
Ferritin	>10000	2890		6627	2029	1404	1283	1345
C7-antigenemia		100/26000		135/22000	1772/23000	61/17000	340/40000	159/20500
β2MG (urine)		1027		6490	2395	205	211	566

Fig. 2 Clinical course

endotracheal intubation was performed because of the development of tachypnea, retraction and low oxygen-saturation. Chest X-ray revealed interstitial pneumonia. Both antiviral drugs were to be ineffective in preventing CMV disease. We were planning his bone marrow transplantation (BMT) using allogeneic stem cells from his brother. On the day we planned that he would enter a clean room, he suddenly died due to cardiac failure (day 76).

Polymerase chain reaction (PCR) to detect CMV was performed in two steps with nested oligonucleotide primers using material from bronchoalveolar lavage fluid (BALF), urine and CSF. The oligonucleotide primers were chosen from conserved regions of the glycoprotein B gene, gB1319 (5TGGAACTGGAACG-TTTGGC3) and gB1604 (5GAAACGCGCGGCAA-TCGG3) amplifying the 293–296 (size varied by strain) bp fragment (Genemed Biotechnologies, Inc, South San Francisco, CA 94080, USA). PCR was done with 1.5 U of Taq polymerase (Perkin-Elmer, Norwalk, CT, USA) during 32 cycles of denaturation (94°C for 1 min), annealing (55°C for 1 min), and extension (72°C for 1 min). The results of his BALF, urine and CSF were positive.

Discussion

Combined immunodeficiency with predominant T cell defect is characterized by functional impairment of T cell immune systems, whereas B cell immune systems are normal[2]. The patients are susceptible to acute and chronic infection in a wide range of organs. CMV is a major pathogen in children with congenital immunodeficiency disorders[3]. This patient showed systemic CMV infection- pneumonia, encephalitis and hepatitis. Numerous inclusion bodies were found in the liver biopsy specimen of the present case. CMV inclusion bodies are usually not found in needle biopsy specimens. We supposed that the presence of CMV inclusion bodies was caused by a marked decrease in T lymphocytes. Since he had severe impairment in cellular immune response, we suggest that the complete lack of inflammatory reaction resulted in numerous inclusion bodies in his liver[4]. In this respect, this case appears to very rare. We supposed heart failure was induced by CMV pericarditis. Moreover, bone marrow findings represented HPS, despite Langerhans cell histiocytosis and hemophagocytic lymphohistiocytosis could not be ruled out.

Both Ganciclovir and Foscarnet were administerd. Ganciclovir is widely used for the prophylaxis and treatment of CMV infection in immunocompromised persons[5]. However prolonged Ganciclovir therapy can lead to the development of Ganciclovir-resistant strains[6]. Wolf et al suggested that the emergence of resistant strains in children with primary combined immunodeficiency appeared earlier than in other groups of CMV-infected patients and that all mutations were detected within 10 days to 3 weeks from the initiation of therapy. Therefore children with primary combined immunodeficiency and CMV infection often deteriorate despite antiviral therapy[7]. In the present case, when Ganciclovir was used for about two weeks, CMV antigen levels elevated. When Foscarnet was given simultaneously, CMV antigen levels slightly decreased, but his consciousness level deteriorated. At first, we suspected that hyponatremia, (110 mEq/L), as a side effect of the antiviral drugs, had led to his drowsiness. However, after hyponatremia was corrected, his

consciousness level remained unchanged. CSF was not cultured for CMV, but PCR detected CMV. We speculated that his drowsiness was induced by CMV encephalitis. CMV infection of the central nervous system has often been found in immunocompromised states, particularly associated with the human immune deficiency virus (HIV)[8].

Despite recent improvements in diagnosis and therapy, CMV infection accompanied with combined immunodeficiency disorders is still associated with high morbidity and mortality. In particular in patients failing on therapy with Ganciclovir and Foscarnet, Cidofovir can be considered as second-line therapy[9]. In some infants with profound immunodeficiency and complete Di George syndrome, transplantation of thymus tissue can restore normal immune function[10]. There are also some reports on treating CMV infection accompanied with combined immunodeficiency disorders by BMT[11] and thymosin (thymic hormone)[12]. The patient suddenly died before BMT which we had been planning to attempt as an aggressive therapy. The development of effective therapies is essential for the treatment of severe immunodeficiency syndrome.

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重症CMV感染症をきたしたcombined immunodeficiency with predominant T cell defectの1例

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【要旨】 我々は発熱と哺乳力低下を主訴とした生後2ヶ月の男児を経験した．汎血球減少と肝機能障害が進行し，CMV抗体価の上昇を認めた．骨髄穿刺では骨髄貪食細胞を認め，肝生検では多数の封入体を示し，血球貪食症候群 (HPS) と思われた．Tcell系の低下を認め，combined immunodeficiency with predominant T cell defectと診断した．抗ウイルス剤 (GancyclovirとFoscarnet) を含めた様々な治療を行うも，CMV抗原陽性細胞の減少を認めず，意識レベルの低下を認め，骨髄移植の準備中に心不全にて死亡した．免疫不全症を基礎にもつ乳児ではCMV感染症は高い罹患率と死亡率を示しており，有効な治療法の確立が必要とされると思われた．

〈**Key words**〉 CMV, Combined immunodeficiency with predominant T cell defect, HPS