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A Case of Castleman's Disease of Hyaline-Vascular Type Associated with Pure Red Cell Aplasia Which was Successfully Treated with Cyclosporine

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Abstract A 70-year-old female complained of palpitation. CBC demonstated anemia and bone marrow aspiration smear demonstrated absence of erythroid hematopoietic cells, and pure red cell aplasia (PRCA) was diagnosed. Computed tomography (CT) demonstrated abdominal tumor. Biopsy of the abdominal tumor showed proliferation of lymph follicles with small and medium-sized lymphocytes, angiofollicular pattern in their center, and hyalinization around the surrounding tissue. Based on these findings, Castleman's disease (CD) of hyaline-vascular (HV) type was diagnosed. Since anemia progressed, a possible relation between the pathogenesis of PRCA and CD was considered. Therefore, prednisolone (PSL) was administered for two months as well as two courses of COP (cyclophosphamide, oncovin and prednisolone) chemotherapy and 40Gy radiation to the abdominal tumor. After these treatments, the size of abdominal tumor decreased, but PRCA did not improve. Subsequently cyclosporine was administered for five months, and was effective for the improvement of anemia. These results indicated the immunological pathogenesis of PRCA even in Castleman's disease of hyaline-vascular type.

Key words: Castleman's disease, hyaline-vascular type, pure red cell aplasia, cyclosporine

Introduction

Castleman's disease (CD) is divided into the hyaline-vascular type (HV) and the plasma cell type (PC), and mixed type.[1-5] The HV type occurs much more frequently than the PC type and mixed type, and is usually localized to the mediastinum or pulmonary hilum.[1-5] The PC type involves lymph nodes separately or in aggregations and often displays multicentricity〔multicentric CD (MCD)〕with systemic symptoms including autoimmune phenomena and complained of fever, anemia and polyclonal hypergammaglobulinemia.[3-5] Few cases of MCD with pure red cell aplasia (PRCA) had been reported, and an immunological mechanism for the pathogenesis of PRCA in MCD had been suggested by the improvement of PRCA with the administration of immunosuppressive agents.[6][7] We experienced a rare case of PRCA in CD of HV type, in whom the systemic symptom and laboratory abnormalities had not been observed. The treatment of PRCA in CD of HV type in the present patient by administration of prednisolone, COP chemotherapy, radiation to abdominal tumor did not improve PRCA, and administration

of cyclosporine was effective for the improvement of PRCA. These results indicated an immunological mechanism for the pathogenesis of PRCA even in the case of Castleman's disease of HD type.

Case report

A 70-year-old female complained of palpitation and general dullness, and consulted a local hospital in middle of November 2007. At that hospital, anemia (Hb 3.2g/dl) was diagnosed, and abdominal tumor was detected by computed tomography (CT). Therefore, the patient was transferred to our hospital for further examinations.

Laboratory data on admission is shown in Table 1. CBC demonstrated anemia, and the counts of platelets and leukocytes and differential of leukocytes were normal. LDH was not elevated. Coombs test (direct and indirect) was negative. Anti-nuclear antibody (ANA) was negative. Bone marrow aspiration smear demonstrated hypocellular marrow with the absence of erythroid hematopoietic cells. Myeloid and megakaryocytic cells were normally present. Plasma level of erythropoietin (Epo) was markedly elevated. Based on these findings, pure red cell aplasia (PRCA) was diagnosed. Antibody for Parvovirus B19; IgG was elevated and IgM was normal, indicating past infection, and Parvovirus DNA in the blood was negative.

CT demonstrated abdominal tumor (8x20cm), around abdominal aorta involving superior mesenteric artery, renal artery and left ureter (Fig. 1). Thymoma was not observed. Biopsy of the abdominal tumor

Table 1 Laboratory data on admission
( ): normal value

CBC		Chemistry	
RBC (x10^4/μl)	101	Total Protein (g/dl)	6.5
Hb (g/dl)	3.2	Albumin (g/dl)	4.1
Ht (%)	10.1	Globulin (g/dl)	2.4
MCV (fl)	100.0	γ -Glb (%)	15.4
MCH (pg)	31.7	Total Bilirubin (mg/dl)	1.2
MCHC (%)	31.7	AST (IU/l)	21
Ret (%)	0.1	ALT (IU/l)	11
Platelet (x10^4/μl)	18.2	LDH (IU/l)	237
WBC (/μl)	2540	ALP (IU/l)	195
N Seg (%)	71.7	BUN (mg/dl)	18
Eo (%)	3.5	Creatinine (mg/dl)	0.7
Ba (%)	2.2		
Lymph (%)	16.5	CRP (mg/dl)	0.1
Mono (%)	6.7	sIL2-R (IU/l) (220-530)	4400
		IL-6 (pg/ml) (<4.0)	12.3
Bone Marrow	Hypocellular	Epo (mU/ml) ((8-30)	1790
Myeloblast (%)	0.8	Ferritin (ng/ml)	3093
Promyelocyte (%)	1.2		
N Myelocyte (%)	20.2	ParvoB19 IgG (<2.0)	8.26
N Metamyelocyte (%)	12.6	ParvoB19 IgM (<0.8)	0.37
N Band (%)	20.2	ParvoB19 (DNA)	(-)
N Seg (%)	17.2		
Eo (%)	1.0	Coombs,direct	(-)
Lymph (%)	20.0	indirect	(-)
Mono (%)	3.0	ANA (<x40)	x40
Plasmocyte (%)	4.0		
Erythroblast			
Basophilic	0		
Poychromatophilic	0		

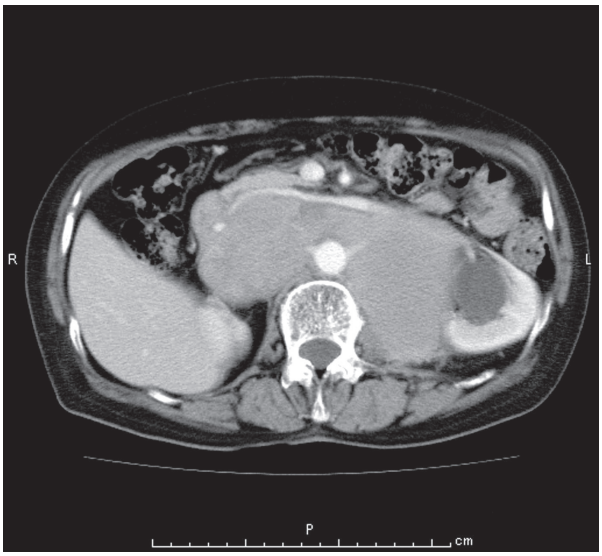

Fig. 1 Computed tomography (CT) of abdomen showing abdominal tumor around the abdominal aorta involving SMA, renal artery and left ureter.

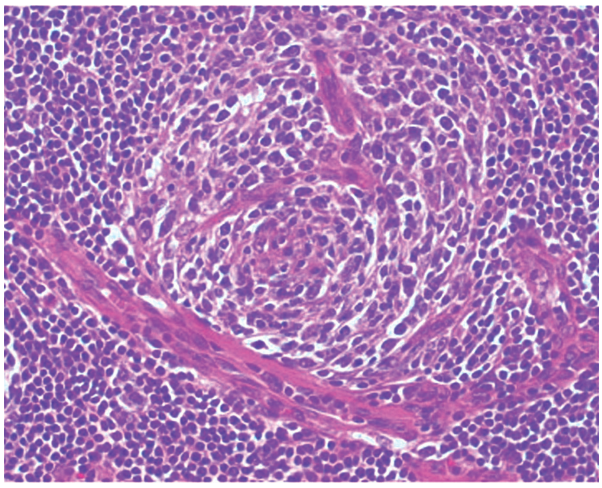

Fig. 2 Microscopic findings of the biopsied abdominal tumor showed proliferation of lymph follicles with small and medium-sized lymphocytes, angiofollicular pattern, and hyalinization. (HE staining, x20).

showed proliferation of lymph follicles with small and medium-sized lymphocytes, angiofollicular pattern and hyalinization (Fig. 2). Marked infiltration of plasma cells indicating PC type was not observed in these specimens. Immunohistochemical staining demonstrated CD3, CD5 and CD45RO positive lymphocyts in the interfollicular areas and CD20 poistive lymphocytes in the follicles. Flow cytometric analysis of the biopsied specimen by CD45 gating demonstrated; CD2 60.8%, CD3 57.3%, CD4 38.7%, CD5 62.9%, CD7 60.1%, CD8 23.5%, CD10 30.5%, CD19 43.3%, CD20 46.0%, CD23 6.3%, κ-chain 4.8% and λ-chain 37.0%. Based on these findings, CD of HV type was diagnosed.

Plasma levels of soluble interleukin-2 receptor (sIL-2 R) was markedly elevated, and interleukin-6 (IL-6) was slightly elevated. Serum γ globulin were not elevated, and CRP was negative.

Clinical Course (Fig. 3)

For the treatment of PRCA, prednisolone (PSL), 30mg/day was administered since the middle of December. However, anemia did not improve and the abdominal tumor did not decrease in size. COP (cyclophosphamide, oncovin and prednisolone) chemotherapy, in which adriamycin was excluded as in standard CHOP chemotherapy for malignant lymphoma, was started in early Feburary 2008 because of the possible pathogenetic relationship between PRCA and CD of HV type, and the size of abdominal tumor decreased somewhat. One more course of COP was given, however, anemia did not improve and abdominal tumor did not show a further decrease in size. Radiation to the abdominal tumor was performed since the middle

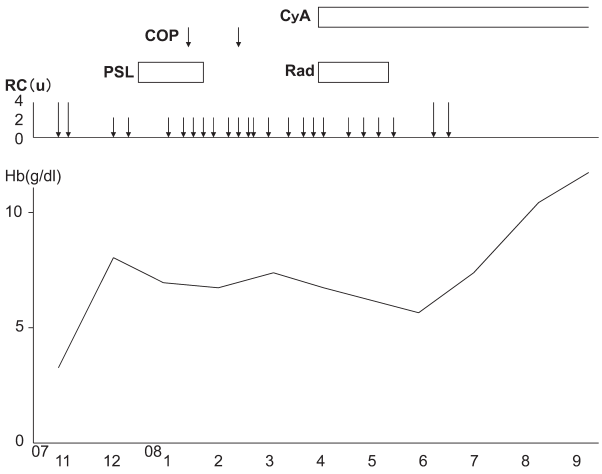

Fig. 3 Clinical course.
RC: red blood cells, PSL: prednisolone, COP: cyclophosphamide, oncovin, prednsiolone, Rad: radiation, CyA: cyclosporine A.

of April, 1.8Gyx22 days and total 40 Gy. After these treatments, the level of sIL-2R decreased, CT and positron emission tomography (PET) studies demonstrate that the abdominal tumor decreased in size (5x3cm), but did not completely disappeared, and PET still demonstrated viability (SUV max:3.4). Anemia did not improve, and two units of red blood cells were transfused every one to two weeks to maintain the level of hemoglobin 7-8g/dl. Finally cyclosporine A (CyA), 200mg/day, was administered starting early of April. Anemia improved after 5 months of cyclosporine administration, and red cell transfusion discontinued. PET demonstrated a further decrease in the abdominal tumor with SUV max 2.7, and the level of sIL-2R decreased to 593 IU/l at the end of May.

Discussion

The diagnosis of PRCA in the present patient was made by anemia, decreased reticulocyte count, absence of erythroid cells in the bone marrow and increased level of plasma Epo. The cause of PRCA is heterogeneous, and several drugs, pregnancy, infections with several viruses such as Parvovirus B19, and lymphoproliferative disorderes had been related with the pathogenesis of PRCA.[8)9)] These causes were excluded in the present patient. Various autoimmune mechanisms of associated PRCA had been described in the lymphoproliferative disorders especially chronic lymphocytic leukemia, non-Hodgkin's lymphomas or large granular lymphocyte (LGL) leukemia; immunological suppression of erythropoiesis by antibodies against red cell precursors and against erythropoietin; T-helper cell-mediated antibody production, MHC-restricted and MHC-unrestricted recognition of red cell progenitors by $\alpha\beta$ or $\gamma\delta$ T-cells; and MHC-unrestricted cytotoxicities by NK cell or T cell.[8)9)]

Few cases of PRCA associated with CD have been reported in MCD of PC type.[6)7)] However, there were no reported cases of PRCA associated with CD of HV type, and the present patient is the first case. We think that PRCA and CD of HV type in the present patient might be pathogenetically related, since these two rare diseases developed simultaneously.

Symptom in CD of HV type may be absent or limited to locus caused by compression due to the mass effect of tumor, differing from those of generalized symptom in MCD.[1-5)] The present patient did not have generalized constitutional symptoms such as fever and autoimmune disease, laboratory abnormalities such as hypergammaglobulinemia was absent, CRP was not elevated and plasma IL-6 level was not markedly elevated as have been observed in MCD.[3-5)]

The increased plasma level of sIL-2R in the present patient represents the pathological nature of lymphoproliefarative disorder of the abdominal tumor, and the level decreased after the treatment. In the present patient, the immunohistochemical study and flow cytometric analysis of the biopsied specimen of abdominal tumor demonstrated positivity for a variety of T and B cell markers, although the rearrangement of immunoglobulin or T-cell receptor gene was not studied, therefore the clonality of the lymphoma cells was not demonstrated.

Therapy for MCD involves administration of alkylating agents or corticosteroids,[3-5)] and recently anti-IL-6 receptor antibody for CD of PC type and MCD type.[10)] Therapy for CD of HV type may not be necessary unless the patient complains of serious symptom. In the present patient, the local symptom with compression by abdominal tumor was not observed, however, PRCA, which was heavily red blood cell transfusion dependent, was complicated. This fact needed some kinds of therapies against PRCA in the present patient. Surgical resection of the abdominal tumor was impossible since the tumor involved the abdominal aorta and superior mesenteric artery.

Pathogenesis of PRCA in MCD may be an immunological mechanism. Two previously reported cases of PRCA in MCD were complicated with amyloidosis, and both PRCA and amyloidosis were successfully treated with methylprednisolone pulse therapy and subsequent PSL administration.[6)7)] We first administrered PSL, then COP chemotherapy without adriamycin and radiation. However, PRCA did not improve although abdominal tumor decreased in size, but remained vi-

able. Finally, cyclosporine was administered, and anemia improved after 5 months of the administration. The abdominal tumor decreased in size and viability, although the tumor persisted. These findings supposed the immunological mechanism in the pathogenesis of PRCA by suppression of erythropoiesis by infiltrating T-cells as well as B-cells even in CD of HV type. Careful observation is necessary for the regrowth of the abdominal tumor. More cases should be collected, and analyzed to determine the detailed pathogenetic mechanism of PRCA in CD of HV type.

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