Clinical Features of Hemophagocytic Syndrome in Patients with Dermatomyositis

NOBUYUKI YAJIMA, KUNINOBU WAKABAYASHI, TSUYOSHI ODAI, TAKEO ISOZAKI, MIZUHO MATSUNAWA, YUSUKE MIWA, MASAO NEGISHI, HIROTSUGU IDE, and TSUYOSHI KASAMA

ABSTRACT. ***Objective.*** To investigate the clinical features of patients with dermatomyositis (DM) complicated by hemophagocytic syndrome (HPS).

Methods. Twenty-four patients diagnosed with DM and treated at our hospital between January 2002 and April 2007 were enrolled for study. Serum levels of various parameters including cytokines were determined during the active disease states.

Results. Levels of serum ferritin, creatine kinase, and immune complexes were all significantly higher in all patients with HPS than in those without HPS. Levels of soluble interleukin-2 receptor, macrophage colony stimulating factor, and the chemokine CX3CL1 were significantly elevated in DM patients with HPS.

Conclusion. Our findings suggest that mechanisms related to both circulating immune complexes and circulating cytokines are involved in the pathogenesis of HPS complicating DM. (First Release July 15 2008; J Rheumatol 2008;35:1838–41)

Key Indexing Terms:
HEMOPHAGOCYTIC SYNDROME DERMATOMYOSITIS CYTOKINE CX3CL1

Hemophagocytic syndrome (HPS), alternatively referred to as secondary hemophagocytic lymphohistiocytosis (HLH)[1] or macrophage activation syndrome (MAS), reflecting cytokine storms[2], is a rare disorder of the mononuclear phagocytic system characterized by systemic proliferation of non-neoplastic histiocytes engaged in abnormal phagocytosis of hematopoietic cells[3]. Common manifestations include high fever, pancytopenia, hepatosplenomegaly, and disseminated intravascular coagulopathy. Although HPS has been associated with autoimmune diseases, few case reports have been published describing HPS in patients with dermatomyositis (DM)[4-7]. We investigated the clinical features of DM complicated by HPS and compared them to the features of DM without HPS.

MATERIALS AND METHODS

All patients who were diagnosed with DM and treated at our hospital between January 2002 and April 2007 were enrolled into our study. The study included 24 patients with DM, according to Bohan and Peter's criteria[8]; in 4 of those patients, DM was complicated by HPS. Muscle biopsy was done in all patients with DM, except in one amyopathic DM patient, with typical pathological changes for DM, such as the presence of inflammatory infiltrates, degenerating and regenerating fibers, and muscle fiber atrophy. The diagnosis of HPS was performed based upon the revised diagnosis criteria by Henter, *et al*[1], with lymph node or bone marrow aspiration.

From the Division of Rheumatology, Department of Internal Medicine, Showa University School of Medicine, Tokyo, Japan.

N. Yajima, MD; K. Wakabayashi, MD; T. Odai, MD; T. Isozaki, MD; M. Matsunawa, MD; Y. Miwa, MD; M. Negishi, MD; H. Ide, MD; T. Kasama, MD, Division of Rheumatology, Department of Internal Medicine, Showa University School of Medicine.

Address reprint requests to Dr. T. Kasama, Division of Rheumatology, Department of Internal Medicine, Showa University School of Medicine, Tokyo, 142-8666, Japan. E-mail: tkasama@med.showa-u.ac.jp

Accepted for publication April 2, 2008.

Serum creatine kinase (CK), aldorase, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), triglyceride, fibrinogen, ferritin, D-dimer, complement hemolysis activity (CH50), anti-Jo-1 antibody, and immune complex (IC-C1q) were determined in the clinical laboratory at our hospital. Serum levels of soluble interleukin-2 receptor (sIL-2R), macrophage colony stimulating factor (MCSF), and the soluble form of CX3CL1 (sCX3CL1) were measured by ELISA kits according to the manufacturer's instructions (R&D Systems, Minneapolis, MN, USA). All human experiments were carried out in accordance with protocols approved by the Human Subjects Research Committee at our institution, and informed consent was obtained from all patients.

The categorical data and differences in serum cytokine levels between the 2 groups were analyzed by Fisher's exact probability test and Mann-Whitney U-test, respectively. Values of $p < 0.05$ were considered significant.

RESULTS

Characteristics of patients with HPS are summarized in Table 1. The 4 patients with DM complicated with HPS were all male. Although 1 case was amyopathic DM (ADM), which satisfied the criteria for definite ADM described by Sontheimer[9], serum levels of CK were elevated in the other 3 cases, and complication of interstitial pneumonitis was seen in 3 cases. Increased serum levels of triglyceride, sIL-2R (sCD25), and D-dimer (in 3 cases) and decreased fibrinogen (in 3 cases), suggesting activated coagulopathy, were found. Symptoms of fever and decreased natural killer cell activity[10] that are included in the revised criteria by Henter, *et al*[1], were seen in DM patients without HPS, but were not examined in our cases; however, our 4 cases fulfilled the revised HPS criteria. Appearance of HPS was during active phase of DM in all cases. Intensive medications including the combination of steroid pulse therapy, immunosuppressants, and intravenous immunoglobulin (IVIG) were needed. Table 2 shows the comparison of clin-

Table 1. Clinical features of HPS* in DM.

Case	1	2	3	4
Age/sex	16/M	36/M	50/M	86/M
Fever (> 38.5° C)	+	+	+	+
Hepatosplenomegaly	+	+	+	+
Laboratory results				
Neutrophils, /μl	2560	865	2280	510
Hb, g/dl	7.7	8.9	8.5	7.8
Platelets, × 10^4/μl	3.9	11.7	7.3	39.2
Triglyceride, mg/dl	635	298	255	387
Fibrinogen, mg/dl	103	144	189	292
D-dimer, μg/ml	8.8	5.4	2.1	< 1.0
Ferritin, ng/ml	2796	2854	585	5329
sIL-2R sCD25 U/ml	882	2930	949	1470
CK, IU/ml	122	11338	5604	3877
Amyopathic DM†	+	–	–	–
Interstitial pneumonitis	+	+	–	+
Appearance of HPS	Active phase of DM	Active	Active	Active
Hemophagocytosis	+[l]	+[b]	+[b]	+[b]
Treatments‡				
Steroid pulse therapy	+	+	+	+
Immunosuppressants	+	+	+	+
IVIG	+	–	+	+
HPS response to treatments	None	Improved	Improved	Partial
Outcome	Rapidly fatal	Recovered	Recovered	Fatal by malignancy

* Henter, *et al* criteria[1]. † Sontheimer criteria[9]. Normal range in serum: triglyceride 40–170 mg/dl; fibrinogen 200–400 mg/dl; D-dimer < 1.0 μg/ml; ferritin 10–190 ng/ml; CK 30–180 IU/l; sIL-2R 220–530 U/ml. ‡ Steroid pulse therapy: 500–1000 mg methylprednisolone bolus IV injection daily for 3 days; immunosuppressants: cyclosporin A, cyclophosphamide, or methotrexate. [b] bone marrow aspiration, [l] lymph node aspiration; HPS: hemophagocytic syndrome; DM: dermatomyositis; CK: creatine kinase; IVIG: intravenous immunoglobulin.

ical features of DM with and without complication by HPS. Levels of serum CK, ferritin, and IC-C1q were significantly higher in all 4 patients with HPS than in those without HPS, suggesting greater DM disease activity, as shown in Table 2. Further, in patients with DM alone, 13 patients received only glucocorticoids, and the other 3 patients were also given immunosuppressants with IVIG agents. Three DM patients with HPS received the combination of high-dose glucocorticoids and immunosuppressive agents with IVIG because of poor response (Table 2). Although serum levels of tumor necrosis factor-α and interferon-γ were little affected when DM was complicated by HPS (data not shown), levels of sIL-2R, MCSF, and sCX3CL1 were significantly elevated (Table 3).

DISCUSSION

The pathogenesis of HPS in patients with autoimmune diseases could involve several different mechanisms. Wong, *et al*, who described acute lupus HPS[11], favored an immune complex-mediated mechanism. In addition, Kumakura, *et al* reported a case of autoantibody-associated reactive hemophagocytosis[12]. We found that the clinical features of the HPS complicating DM differ from the aforementioned cases in that they involve severe systemic symptoms and required intensive therapy, such as a combination of glucocorticoids and immunosuppressants with IVIG, due to the exacerbation of DM disease activity, which suggests an immune complex-mediated mechanism with cytokine storms. These patients also show elevated levels of MCSF and sIL-2R, suggesting activation of macrophages and T cells, respectively. Interestingly, we also observed that serum sCX3CL1 levels were significantly higher in patients with DM (6048.3 pg/ml) than in healthy individuals (92.3 pg/ml), and that sCX3CL1 levels in patients with DM complicated by HPS (14,332.8 pg/ml) were significantly higher than in those without HPS (4391.4 pg/ml). CX3CL1 has been implicated in the pathogenesis of inflammatory myositis[13], rheumatoid arthritis[14], and rheumatoid vasculitis[15], and its elevation is indicative of endothelial cell activation.

Collectively, our observations suggest that systemic activation of macrophages, T cells, and endothelial cells, along with a dysregulated immune complex-mediated mechanism, is involved in the pathogenesis of HPS in DM. Rheumatologists should consider the possibility of HPS when acute cytopenia is seen in patients with DM, and intensive therapy comprising immunosuppressants and IVIG in combination with relatively high doses of glucocorticoids should be introduced.

Table 2. Comparison of clinical features of DM with and without complication by HPS. Clinical measures were determined when the sign of HPS appeared in active DM (usually a few weeks after DM diagnosis). Measures in DM patients without HPS were determined at the active (newly diagnosed, untreated) phase of disease.

	DM complicated by HPS	DM without HPS
Patients male/female	4 (4/0)*	20 (8/12)
Age	47.5 ± 14.6	58.4 ± 4.3
Fever (%)	4 (100)	7 (31.8)
Arthralgia (%)	4 (100)*	7 (31.8)
Skin lesion (%)		
Heliotrope sign	1 (25)	13 (65)
Gottron's sign	1 (25)	18 (90)
Shawl sign	2 (59)	5 (25)
V neck sign	2 (50)	5 (25)
Interstitial pneumonitis (%)	3 (75)	10 (50)
Splenomegaly (%)	3 (75)	1 (5)
Malignancy (%)	1 (25)	7 (35)
Panniculitis (%)	0 (0)	1 (5)
Cytopenia > 2 cell lineages (%)	4 (100)	1 (5)
CRP, mg/dl	1.6 ± 0.5	2.5 ± 1.2
ESR, mm/h	58.5 ± 18.0	57.2 ± 7.6
CK, IU/l	5235.3 ± 2334.0*	1518.2 ± 284.4
Aldorase, IU/L	21.4 ± 6.5	13.7 ± 2.7
Triglyceride, mg/dl	393.8 ± 1.70	160.7 ± 129.0
Fibrinogen, mg/dl	182.0 ± 81.3	271.9 ± 100.2
Anti-Jo-1 antibody positive (%)	0 (0)	1 (5)
CH50, U/ml	35.4 ± 7.4	48.8 ± 1.8
Immune complex (IC-C1q) μg/ml	1.8 ± 1.0*	0 ± 0
Ferritin ng/ml	2891.0 ± 969.2*	986.7 ± 207.3
Treatments (%)		
High doses of glucocorticoids†	4 (100)	13 (65)
Immunosuppressants	4 (100)	8 (40)
IVIG	3 (75)	7 (35)
Combination of above 3 therapies	3 (75)	3 (15)

† Over 1.2 mg/kg body weight/day prednisolone, including steroid pulse therapy. * $p < 0.05$ vs DM without HPS. DM: dermatomyositis; HPS: hemophagocytic syndrome; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; CK: creatine kinase; CH: hemolytic complement; IVIG: intravenous immunoglobulin.

Table 3. Serum levels of cytokines and soluble IL-2 receptors† of DM with and without complications by HPS. Measures in serum were determined when the sign of HPS appeared in active DM (usually a few weeks after DM diagnosis). Measures in DM patients without HPS were determined at the active (newly diagnosed, untreated) phase of disease.

	DM complicated by HPS	DM without HPS
sIL-2R, U/ml	1557.8 ± 475.9*	704.4 ± 112.3
MCSF, pg/ml	8994.7 ± 4009.6*	1742.2 ± 337.9
sCX3CL1, pg/ml	14332.8 ± 3671.7*	4391.4 ± 1606.6

† Measured by ELISA. * $p < 0.05$ vs DM without HPS. DM: dermatomyositis; HPS: hemophagocytic syndrome; MCSF: macrophage colony stimulating factor.

REFERENCES

1. Henter JI, Horne A, Arico M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124-31.
2. Grom AA. Macrophage activation syndrome and reactive hemophagocytic lymphohistiocytosis: the same entities? Curr Opin Rheumatol 2003;15:587-90.
3. Larroche C, Mouthon L. Pathogenesis of hemophagocytic syndrome (HPS). Autoimmun Rev 2004;3:69-75.
4. Yasuda S, Tsutsumi A, Nakabayashi T, et al. Haemophagocytic syndrome in a patient with dermatomyositis. Br J Rheumatol 1998;37:1357-8.
5. Kobayashi I, Yamada M, Kawamura N, Kobayashi R, Okano M, Kobayashi K. Platelet-specific hemophagocytosis in a patient with juvenile dermatomyositis. Acta Paediatr 2000;89:617-9.
6. Madaule S, Porte L, Couret B, Arlet-Suau E. Fatal haemophagocytic syndrome in the course of dermatomyositis with anti-Mi2 antibodies. Rheumatology Oxford 2000;39:1157-8.
7. Sterba G, Rodriguez C, Sifontes S, Vigilanza P. Macrophage activation syndrome due to methotrexate in a 12-year-old boy with dermatomyositis. J Rheumatol 2004;31:1014-5.

8. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med 1975;13;292:344-7.
9. Sontheimer RD. Cutaneous features of classic dermatomyositis and amyopathic dermatomyositis. Curr Opin Rheumatol 1999;11:475-82.
10. Gonzalez-Amaro R, Alcocer-Varela J, Alarcon-Segovia D. Natural killer cell activity in dermatomyositis-polymyositis. J Rheumatol 1987;14:307-10.
11. Wong KF, Hui PK, Chan JLC. The acute lupus hemophagocytic syndrome. Ann Intern Med 1991;114:387-90.
12. Kumakura S, Ishikura H, Umegae N. Autoimmune-associated hemophagocytic syndrome. Am J Med 1997;102:113-5.
13. Suzuki F, Nanki T, Imai T, et al. Inhibition of CX3CL1 (fractalkine) improves experimental autoimmune myositis in SJL/J mice. J Immunol 2005;175:6987-96.
14. Ruth JH, Volin MV, Haines GK 3rd, et al. Fractalkine, a novel chemokine in rheumatoid arthritis and in rat adjuvant-induced arthritis. Arthritis Rheum 2001;44:1568-81.
15. Matsunawa M, Isozaki T, Odai T, et al. Increased serum levels of soluble fractalkine (CX3CL1) correlate with disease activity in rheumatoid vasculitis. Arthritis Rheum 2006;54:3408-16.