

Case Report

**Hemophagocytic syndrome associated with rheumatoid arthritis:
A case report and review of the literature**

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Running title: RA with hemophagocytic syndrome

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Abstract

We report a patient with rheumatoid arthritis (RA) who showed bicytopenia with hyperferritinemia and hepatic dysfunction ascribable to hemophagocytic syndrome (HPS) 2 weeks after commencement of bucillamine. Pathology of the bone marrow showing infiltration of macrophages confirmed the diagnosis of HPS. On the basis of renal dysfunction with an increase in fibrin degradation products, disseminated intravascular coagulation was considered to be concurrent with HPS. Oral prednisolone and cyclosporine A were started right after cessation of bucillamine, and yielded complete normalization of hepatic and renal function and hematology. As there was neither disease activity of RA nor associated infection throughout the clinical course, bucillamine was suspected of being the cause of HPS in our patient. HPS is a very rare complication in RA, but should be actively considered when abnormalities in laboratory data, especially pancytopenia and hepatic dysfunction, quickly worsen.

Key words: rheumatoid arthritis, bucillamine, corticosteroid, cyclosporine A, disseminated intravascular coagulation, hemophagocytic syndrome

Introduction

Hemophagocytic syndrome (HPS) is a potentially life-threatening disorder characterized clinically by pancytopenia and liver dysfunction ascribable to profound activation of macrophages mainly in the bone marrow. It is well known that infection by microorganisms, such as the Epstein-Barr virus (EBV), malignancies, and acquired or congenital immunodeficiencies sometimes induce HPS. Autoimmune disorders, particularly systemic lupus erythematosus (SLE) and adult-onset Still's disease, can also occasionally cause HPS (1). Here, we report a patient with HPS complicating rheumatoid arthritis (RA). Bicytopenia with hyperferritinemia and liver dysfunction typical of HPS developed 2 weeks after commencement of bucillamine, and after cessation of this drug the administration of corticosteroid and cyclosporine A cured the patient. RA is an autoimmune disease rarely underlying HPS (2-4). In this report we review the literature and focus upon the pathogenesis of HPS associated with RA.

Case report

A 52-year-old woman suddenly developed polyarthralgia resistant to non-steroidal anti-inflammatory drugs (NSAIDs) with no precipitating cause or significant family history. Three months later she was diagnosed as having RA on the basis of symmetrical swelling with mild tenderness in multiple joints, including bilateral knees and hands, and a positive rheumatoid factor (RF) (169 IU/ml, normal <10 IU/ml) in serum (5). In the classification of severity and the global functional status in RA, she was considered to belong to stage 1 and class 1, respectively (6, 7). She showed no signs or symptoms suggestive of other associated

collagen diseases, but the anti-nuclear antibody with a speckled pattern was positive ($\times 1280$, normal $< \times 40$). Matrix metalloproteinase-3 (80 ng/ml, normal 17.3-59.7 ng/ml) and IgG (2034 mg/dl, normal 870-1700 mg/dl) in serum were increased slightly, and IgA (344 mg/dl, normal 110-410 mg/dl) and IgM (122 mg/dl, normal 35-220 mg/dl) were within normal limits. Although KL-6 in serum was slightly high (683 U/ml, 105-401 U/ml), no abnormal findings were detectable in the chest roentgenogram. Salazosulfapyridine was unusable because of adverse effects such as systemic rash with severe itching, and she was given bucillamine at a dose of 200 mg/day in addition to NSAIDs. There were no abnormal findings in the routine laboratory data right before commencement of bucillamine suggestive of renal or hepatic dysfunction.

Polyarthralgia gradually improved, but she suddenly manifested vomiting and diarrhea with general malaise and intermittent low-grade fever approximately 2 weeks after commencement of bucillamine. On admission to our hospital, physical examination showed no hepatosplenomegaly or lymphadenopathy. Laboratory data demonstrated decreases in white blood cells (2,050/ μ l, normal 3,040-8,720/ μ l) and platelets (5.6×10^4 / μ l, normal 13.7 - 37.8×10^4 / μ l) and increases in total bilirubin (2.33 mg/dl, normal 0.3-1.2 mg/dl), aspartate aminotransferase (390 U/l, normal 12-37 U/l), alanine aminotransferase (203 U/l, normal 7-45 U/l), alkaline phosphatase (1715 U/l, normal 124-367 U/l), γ -glutamyl transpeptidase (287 U/l, normal 6-30 U/l), blood urea nitrogen (35 mg/dl, normal 9-22 mg/dl), creatinine (1.8 mg/dl, normal 0.4-0.8 mg/dl), triglyceride (290 mg/dl, normal 30-150 mg/dl), lactate dehydrogenase (LDH, 2,681 U/l, normal 114-220 U/l) and ferritin (19,668 ng/ml, normal 10-120 ng/ml). Differentiation of WBC was normal. C-reactive protein (CRP, 15.57

mg/dl, normal <0.10 mg/dl) was markedly elevated along with an increase in D-dimer of fibrin degradation products (FDP) (139.5 μ g/ml, normal <1.0 μ g/ml). Soluble interleukin (IL)-2 receptor (5040 U/ml, 135-483 U/ml) and IL-6 (96.3 pg/ml, normal <2.41 pg/ml) in serum were increased markedly. The anti-nuclear antibody (\times 1280) and RF (135 IU/ml) were positive as in the previous examination, but other specific autoantibodies, including anti-double-stranded DNA, anti-SS-A, and anti-SS-B antibodies, were undetectable. Both the direct Coombs' test and anti-platelet antibody were negative. The chest roentgenogram and electrocardiogram were normal. Bone marrow aspirates demonstrated many hemophagocytic macrophages (Fig.1). Intensive survey for infection showed no significant increases in serum antibodies against any agents, including EBV, cytomegalovirus, and herpes simplex virus, or elevation of β -D-glucan. There were no abnormal findings in either computed tomography of the chest and abdomen or upper gastrointestinal endoscopy suggestive of malignancies.

Bucillamine was discontinued soon after admission, and prednisolone and cyclosporine A were started at a dose of 60 mg/day and 150 mg/day, respectively, in addition to antibiotics, intravenous immunoglobulin, anti-thrombin III and gabexate mesilate. Blood culture for bacteria was negative throughout the clinical course. Her clinical symptoms quickly disappeared in conjunction with an increase in platelets and decreases in CRP and LDH (Fig. 2). Hematology and indices of the liver and kidneys were completely normalized within 3 weeks after admission. She was discharged from our hospital 1 month after admission, and prednisolone and cyclosporine A have been tapered in the outpatient clinic. She has remained in good general condition with no arthralgia ascribable to RA at 10 mg/day of prednisolone alone for 3 years to date.

Discussion

The present patient showed bicytopenia in hematology, hepatic dysfunction, increased inflammatory reactions, hypertriglyceridemia and hyperferritinemia, leading to a clinical diagnosis of HPS (8, 9). Bone marrow aspirates showing many hemophagocytic macrophages confirmed this diagnosis (8, 9). HPS is classified into primary and secondary forms, and the lack of a significant family history indicating immunodeficiency suggests that the HPS in our patient belonged to the latter (10). HPS is characterized clinically by high fever (8, 9), but its secondary form often does not show this symptom, as in our patient (11). Considering that renal dysfunction and a remarkable increase in FDP D-dimer were also present, disseminated intravascular coagulation (DIC) was probably associated with HPS. As the routine laboratory data showed no abnormal findings 2 weeks before admission, HPS and DIC seems to have developed and quickly worsened during this short period. Both disorders may have increased the endogenous production of corticosteroid, resulting in remission of polyarthritis due to RA on admission to our hospital. Intensive treatment, including oral prednisolone and cyclosporine A, showed a good therapeutic effect on both HPS and DIC in our patient, and clinical symptoms quickly disappeared in conjunction with normalization of laboratory data.

The pathogenesis of HPS in the present patient remains unclear, but there are 4 possible etiologies. The first is malignancy. Malignant lymphoma and visceral organ carcinoma sometimes cause HPS (4), but in our patient a systemic survey, including CT and endoscopy, demonstrated no abnormal findings suggestive of associated malignancies. The second is an infection. It has been widely recognized that infectious agents, particularly viruses, can cause

HPS (4, 12). Our patient, however, showed negative results in blood culture for bacteria and no significant increases in the antibody titer against viruses, including EBV. There was no evidence suggesting that infection may have played a role in the pathogenesis, although antibiotics and intravenous immunoglobulin were given for a short period at the onset of disease. The third is RA itself. HPS is sometimes associated with autoimmune disorders, particularly SLE and adult-onset Still's disease (1, 4, 13), but rarely with RA. The clinical profiles of our patient and 10 previously described cases of HPS associated with RA are shown in Table 1 (2-4, 14-19). Preceding infection by microorganisms, such as EBV and cytomegalovirus, was confirmed in 4 patients, and only 3 developed HPS in conjunction with a high disease activity of RA. The development of HPS in our patient was considered to be unrelated to RA itself because the activity of this disease was depressed on admission to our hospital.

The fourth possible etiology is a drug. Several recent reports have demonstrated that anti-epileptic agents (20, 21), antibiotics (22, 23) and anti-rheumatic drugs (3, 24, 25) can act as a trigger for HPS. Anti-rheumatic drugs inducing HPS comprise methotrexate and etanercept. The clinical profiles of our patient and 8 previously described cases of drug-induced HPS are shown in Table 2 (3, 20-25). Seven of the 8 previously described cases showed development of HPS in 1 to 2 weeks after commencement of the drugs. HPS in our patient also occurred 2 weeks after commencement of bucillamine, and this drug was considered to play a central role in the pathogenesis. The appearance of systemic rash with itching after administration of salazosulfapyridine may also support this hypothesis with regard to drug intolerance. Hypersensitivity to drugs may cause a systemic inflammatory

response with activation of macrophages and excessive production of cytokines, and lead to the development of HPS as in the present patient (22), although the precise mechanisms remain unclear.

In conclusion, HPS complicates RA with various etiologies, including infections, malignancies, RA itself and drugs. Drug-induced HPS should be actively considered as a possible complication when pancytopenia and liver dysfunction quickly worsen irrespective of the disease activity of RA during treatment with anti-rheumatic drugs, such as bucillamine, methotrexate and etanercept.

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Figures legends

Figure 1: Bone marrow aspirates showing hemophagocytic macrophage.

Figure 2: Clinical course of the patient. CRP: C-reactive protein, LDH: lactate dehydrogenase,

PLT: platelet

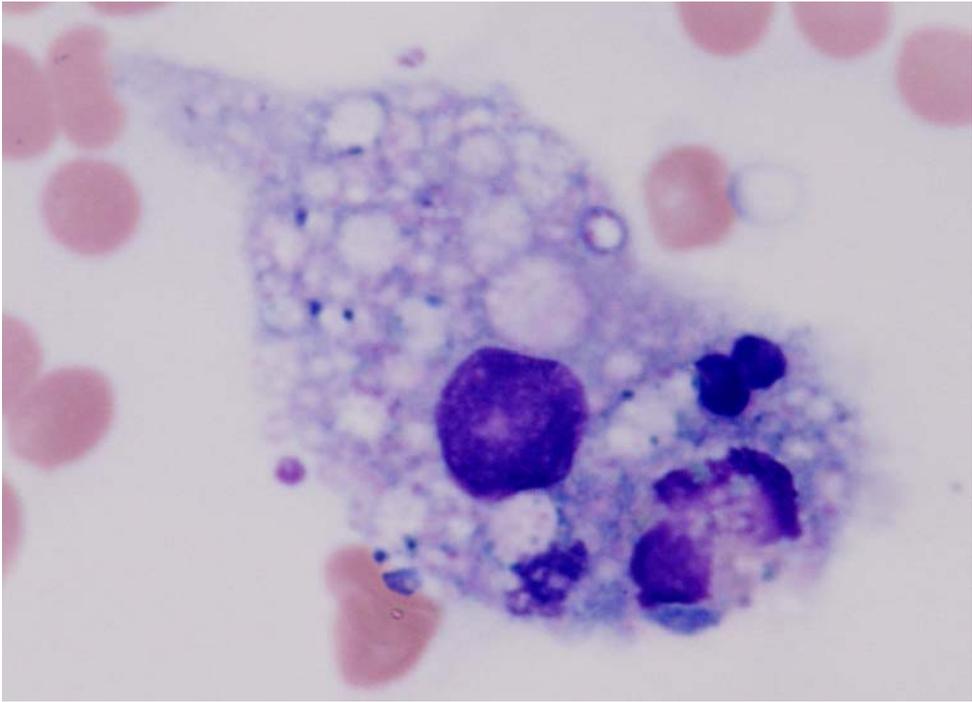


Figure 1

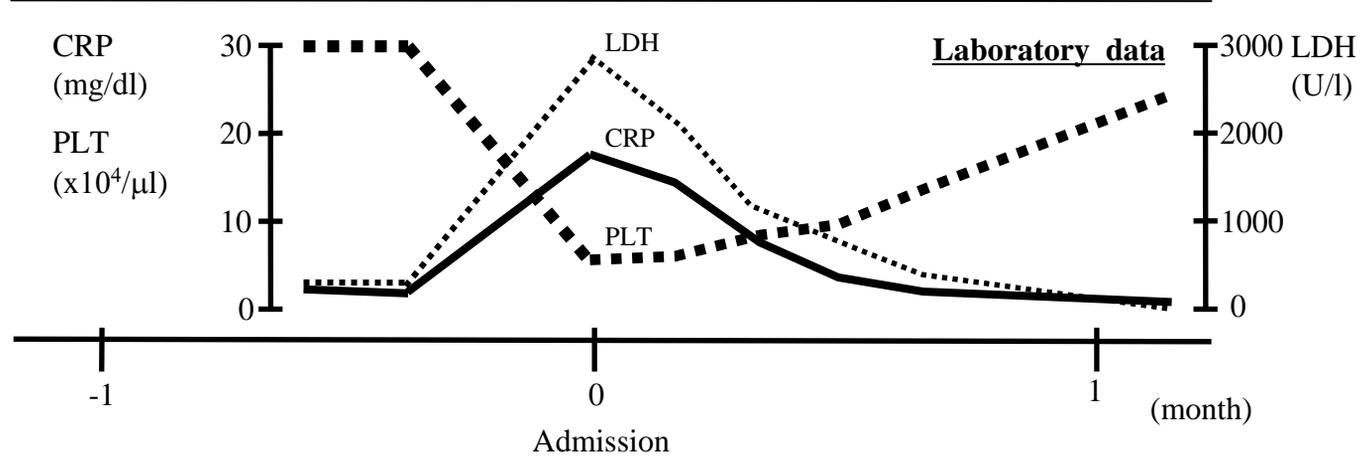
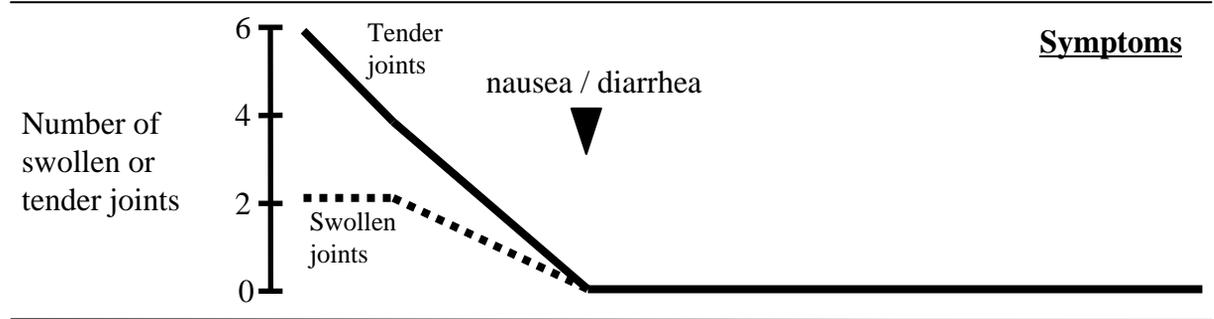
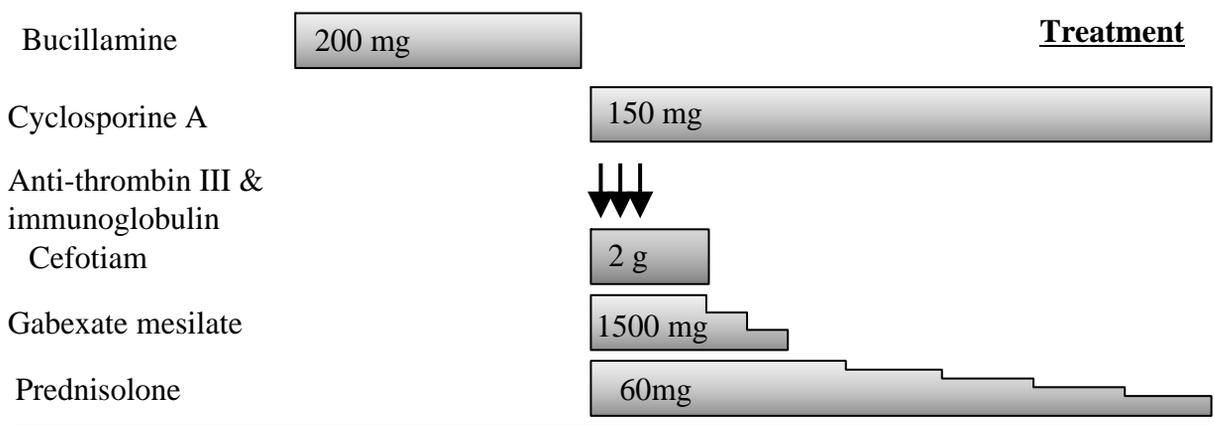


Figure 2

Table 1. Clinical profiles of our patient and previously described cases of hemophagocytic syndrome (HPS) associated with rheumatoid arthritis (RA)

Report	Age/ Sex	Treatment for RA	RA activity	Preceding infection	Treatment for HPS	Outcome
Onishi, 1994 [12]	63/F	ND	ND	EBV	PSL 40mg/day	Improved
Yamanouchi, 1998 [2]	62/ M	MTX	(+)	(-)	CS	Improved
Hashimoto, 1998 [13]	20/F	ND	(-)	ND	CS	Improved
Shibilia, 1998 [14]	64/F	MTX, SASP, CS	(-)	Escherichia coli	Antibiotics	Improved
Kuyama, 2000 [15]	61/F	MTX, CS	(-)	CMV	CS, IVIg	Improved
Sekiuchi, 2003 [16]	65/F	MTX, CS, NSAID	(-)	CMV	CS, IVIg	Improved
Niang, 2004 [17]	ND	ND	ND	ND	CS	Improved
Kumakura, 2004 [4]	64/F	NSAID	(+)	(-)	CS	Partially improved
	69/F	NSAID	(+)	(-)	CS, G-CSF, CyA	Improved
Sandhu, 2007 [3]	42/F	Etanercept, CS, NSAID	(-)	(-)	CS, CyA, IVIg	Died*
Our patient	57/F	BC, NSAID	(-)	(-)	CS, antibiotics, IVIg, CyA	Improved

*Died of acute respiratory distress syndrome and multiorgan failure considered due to sepsis and HPS.

BC: bucillamine, CMV: cytomegalovirus, CS: corticosteroid, CyA: cyclosporine A, EBV: Epstein-Barr virus, G-CSF: granulocyte-colony stimulating factor, IVIg: intravenous immunoglobulin, MTX: methotrexate, ND: not described, NSAID: non-steroidal anti-inflammatory drug, SASP: salazosulfapyridine

Table 2. Clinical profiles of our patient and previously described cases of drug-induced hemophagocytic syndrome (HPS)

Report	Age/ Sex	Primary disease	Drug(s) suspected as a cause of HPS	Interval between commencement of drug(s) and onset of HPS	Treatment for HPS	Outcome
Gutierrez- Rave Pecero, 1991 [18]	9/M	ND (Epilepsy?)	Phenytoin	2 weeks	CS	Improved
Ravelli, 2001 [22]	6/F	Juvenile idiopathic arthritis	Methotrexate	1 day	CyA	Improved
Lambotte, 2002 [20]	45/F	Superficial abscess	Vancomycin, Teicoplanin	10 days	CS	Improved
	53/F	Pneumocystis carinii pneumonia	Trimethoprim/ Sulfamethoxazole	9 days	IVIg	Improved
Ramanan, 2003 [23]	8/F	Juvenile rheumatoid arthritis	Etanercept	2 weeks	CS	Improved
Jain, 2004 [21]	22/M	Tuberculous lymphadenitis	REP, INH, PZA	2 weeks	(-)	Improved
Yang, 2004 [19]	8/M	Epilepsy	Lamotrigine	2 weeks	CS, IVIg	Improved
Sandhu, 2007 [3]	42/F	Rheumatoid arthritis	Etanercept	2 months	CS, CyA, IVIg,	Died
Our patient	57/F	Rheumatoid arthritis	Bucillamine	2 weeks	CS, antibiotics, IVIg, CyA	Improved

CS: corticosteroid, CyA: cyclosporine A, INH: isoniazid, IVIg: intravenous immunoglobulin,
ND: not described, PZA: pyrazinamide, REP: rifampicin