European Review for Medical and Pharmacological Sciences 2012; 16: 1414-1424

Haemophagocytic syndrome in rheumatic patients. A systematic review

M. ATTERITANO[1], A. DAVID[2], G. BAGNATO[1], C. BENINATI[3], A. FRISINA[4], C. IARIA[5], G. BAGNATO[1], A. CASCIO[6]

[1]Department of Internal Medicine, University of Messina, Policlinico G. Martino, Messina, Italy
[2]Department of Neurosciences, Psichiatric and Anesthesiological Sciences, University of Messina, Italy
[3]Elie Metchnikoff Department, University of Messina, Messina, Italy
[4]Dipartimento Materno Infantile, Policlinico G. Martino, Messina, Italy
[5]Infectious Diseases Unit, Azienda Ospedaliera Piemonte-Papardo, Messina, Italy
[6]Tropical and Parasitological Diseases Unit, Department of Human Pathology, Policlinico G. Martino, Messina, Italy

Abstract. – BACKGROUND: Hemophagocytic lymphohistiocytosis (HLH), is a potentially fatal hyperinflammatory syndrome characterized fever, hepatosplenomegaly, and cytopenias. HLH can be either primary, with a genetic aetiology, or secondary, associated with malignancies, autoimmune diseases, or infections. Among rheumatic disorders, HLH occurs most frequently in systemic juvenile idiopathic arthritis.

AIM: To draw attention on this severe syndrome that may often go undiagnosed in patient with rheumatic diseases.

MATERIALS AND METHODS: PubMed search was performed by combining the terms (haemophagocytic, haemophagocytosis, hemophagocytosis, hemophagocytic, erythrophagocytosis, macrophage activation syndrome) and (rheumatic, rheumatologic, arthritis, lupus, Sjögren's syndrome, scleroderma, polymyositis, dermatomyositis, polymyalgia rheumatic, mixed connective tissue disease, polychondritis, sarcoidosis, polyarteritis nodosa, Henoch-Schönlein, serum sickness, wegener's granulomatosis, giant cell arteritis, temporal arteritis, Takayasu's arteritis, Behçet's syndrome, Kawasaki, Buerger's).

RESULTS: 117 papers describing 421 patients were considered. HLH was described in systemic lupus erythematosus in 94 patients, in Still's disease in 37 patients, in rheumatoid arthritis in 13 patients, in systemic juvenile arthritis in 219 patients, in dermatomyositis in 7 patients, in Kawasaki disease in 25 patients, in systemic sclerosis in 5 patients, in Behcet disease in one patient, in polyarteritis nodosa in 6 patients, in ankylosing spondylitis in 2 patients, in mixed connective tissue disease in one patient, in sarcoidosis in 5 patients, in Sjögren's syndrome in 3 patients, in Wegener's granulomatosis in one patient, and in unclassifiable disorders in two patients.

CONCLUSIONS: HLH occurring in the course of rheumatic diseases is an important and often underdiagnosed clinical entity, which can affect prognosis.

Key Words:
Hemophagocytic lymphohistiocytosis (HLH), Zoonoses, Developing countries, Epidemiology, Review.

Introduction

Rheumatic diseases are frequent chronic conditions that impose a great burden to society in terms of losses in quality of life and cumbersome dependency[1]. Although they are considered benign diseases as a whole, some rheumatic diseases may nevertheless be mortal, especially those characterized by severe inflammation[2].

Hemophagocytic lymphohistiocytosis (HLH), is a potentially fatal hyperinflammatory syndrome that is characterized by histiocyte proliferation and hemophagocytosis. The most typical presenting signs and symptoms are fever, hepatosplenomegaly, and cytopenias. Less frequently observed clinical findings are neurological symptoms, lymphadenopathy, edema, skin rash, and jaundice[3,4]. Common laboratory findings include hypertriglyceridemia, hyperferritinemia, a coagulopathy with hypofibrinogemia, and elevated aminotransferases[3,4]. However, HLH should be diagnosed using clinical criteria developed by the Study Group of the Histiocyte Society (Table I)[5,6]. Two forms of the syndrome have been well characterized: a familial HLH and secondary HLH. The diagnosis of familial HLH requires either a positive family history of HLH or the presence of genetic mutations, such as perforin gene mutations[7].

The pathogenesis is poorly understood. However, the strong link between systemic inflammatory syndrome response and haemophagocytosis coupled with peripheral T-cell expansion

Corresponding Author: Antonio Cascio, MD; e-mail: acascio@unime.it

Table I. HLH 2004 Diagnostic criteria (modified from ref.[5,6]).

The diagnosis of HLH can be established if one of either 1 or 2 below is fulfilled:

1. A molecular diagnosis consistent with HLH
2. Diagnostic criteria for HLH are fulfilled (five out of the eight criteria below):
   - Fever
   - Splenomegaly
   - Cytopenias (affecting ≥ 2 lineages in the peripheral blood):
     - Hemoglobin < 90 g/l (in infants < 4 weeks: hemoglobin < 100 g/l
     - Platelets < 100.000/ml
     - Neutrophils < 1000/ml
   - Hypertriglyceridemia and/or hypofibrinogenemia:
     - Fasting triglycerides ≥ 265 mg/dl
     - Fibrinogen ≤ 1.5 g/L
   - Hemophagocytosis in bone marrow or spleen or lymphnodes
   - Low or absent NK-cell activity
   - Ferritin ≥ 500 μg/l
   - Soluble CD25 ≥ 2400 U/L

Comments:

1. If hemophagocytic activity is not proven at the time of presentation, further search for hemophagocytic activity is encouraged. If the bone marrow specimen is not conclusive, material may be obtained from other organs. Serial marrow aspirates over time may also be helpful
2. The following findings may provide strong supportive evidence for the diagnosis: (1) spinal fluid pleocytosis (mononuclear cells) and/or elevated spinal fluid protein, (2) histological picture in the liver resembling chronic persistent hepatitis (biopsy)
3. Other abnormal clinical and laboratory findings consistent with the diagnosis are: cerebromeningeal symptoms, lymph node enlargement, jaundice, edema, skin rash. Hepatic enzyme abnormalities, hypoproteinemia, hyponatremia, VLDL ↑, HDL ↓

and deficient natural killer (NK) activity often found in patients with HLH strongly supports the hypothesis of a defective regulation in the inflammatory and immune response[8]. Thus, as in infection-associated hyperinflammatory syndromes activation of receptors and cells of the innate immunity system is likely to play a major role in HLH[9-12].

Secondary HLH, called also macrophage activation syndrome (MAS), may develop at any age and can occur during systemic infection, immunodeficiency or malignancy[3,14]. Among rheumatic disorders, MAS occurs most frequently in systemic juvenile idiopathic arthritis (sJIA). In sJIA, MAS belongs to the clinical picture of disease being present in subclinical form in 30-40% of patients, whereas the overt form occurs in 10-20%[15]. Moreover, in patients with sJIA, several mutations possibly related to HLH have been recently reported[16,17]. However, application of the HLH-2004 protocol to MAS/HLH secondary to sJIA may be imperfect. In fact, the clinical features of MAS/HLH secondary to sJIA, may differ from those seen in other forms of HLH[18].

In addition, in recent years this syndrome has been increasingly reported in patients with juvenile systemic lupus erythematosus (SLE)[19,20-22], Still's disease[21,23] and other rheumatic disorders[21,24-29].

Because HLH is a serious condition that can follow a rapidly fatal course, its prompt recognition is imperative[30]. The purpose of this systematic review is to draw attention on this severe syndrome that may often go undiagnosed in patient with rheumatic diseases.

Literature Review

PubMed search of human cases of HLH occurring during rheumatic diseases was performed by combining the terms (haemophagocytic, haemophagocytosis, hemophagocytosis, hemophagocytic, erythrophagocytosis, macrophage activation syndrome) and (rheumatic, rheumatologic, arthritis, lupus, Sjögren's syndrome, scleroderma, polymyositis, dermatomyositis, polymyalgia rheumatic, mixed connective tissue disease, polychondritis, sarcoidosis, polyarteritis nodosa, Henoch-Schönlein, serum sickness, Wegener's granulomatosis, giant cell arteritis, temporal arteritis, Takayasu's arteritis, Behçet's syndrome, Kawasaki, Buerger's) for the period January 1990 to August 2012. References were also checked for relevant articles, including review papers. A study was considered eligible for inclusion in the systematic review if it reported data on patients with rheumatic diseases who had microscopic signs of haemophagocytosis and/or fulfilled the diagnostic criteria of Study Group of the Histiocyte Society.

Results

The PubMed search identified 580 papers. Duplicate publications or paper not reporting clinical cases were excluded. After scrupulous analysis, 117 papers describing 421 patients were further evaluated. These papers have been categorized on the basis of rheumatic diseases and are listed in Table II together with a brief comment. HLH was described in systemic lupus erythematosus (SLE) (94 patients)[19-23,31-57], Still's disease (37 patients)[21,23,58-73], rheumatoid arthritis (RA) (13 patients)[21,23,74-83], systemic juvenile arthritis (S-JRA) (219 patients)[15,22,30,31,48,84-102] dermatomyositis (7 patients)[24,103-108], Kawasaki disease (25 patients)[25,48,109-123], systemic sclerosis (SSc) (5 pa-

Table II. Papers describing cases of HLH in the course of rheumatic diseases.

Systemic disease	References and note	N° parer/ cases	
SLE	[19]Retrospective study, 15 cases; [20]Retrospective study, 15 patients; [21]retrospecive study, 14 cases; [22]retrospective study, 19 children; [31]retrospective, 2 children; [23]3 cases; [32]18-year old female, lupus mesenteric vasculitis, EBV reactivation; [33]36 year-old woman; [34,35]antiphospholipid antibodies; [36,37]21-year-old man, HLH and SLE simultaneously; [38,39,40]58-year-old female, interstitial pneumonia, CMV. Gancyclovir resolved the pancytopenia, pneumonia, and fever; 41 non-Hodgkin's lymphoma; [42,43,44]35-year-old woman, Graves' disease, parvovirus B19; [45]28-year-old woman; [46]38-year-old woman; [47]EBV lupus nephritis; [48,49]44-year-old woman, corticosteroid and cyclophosphamide, lupus nephritis, CMV colitis; [50]CMV-induced hemophagocytic syndrome and colitis; [51,52]Successful use of etanercept; [53,54]Successful use of infliximab; [55]pregnant patient, preeclampsia cerebral hemorrhage; [56]2 cases, one after parturition, the other after abortion; [57]33-year-old woman, 3 weeks after parturition	32	94
Still's disease	[58]Adult patient, interstitial pneumonia with pneumomediastinum/recurrent pneumothorax; [59]49-year-old woman; [60]8-year-old child, acute respiratory failure, coagulopathy [61]after initiation of sulfasalazine; [62]2 cases; [63]46-year old woman, high-dose steroid treatment; [64]CMV; [65]50-year-old female, steroids and antimalarial drugs; [66]six patients, one death due to pneumonia, one etanercept; [21]retrospective study 4 cases; [23]retrospective study 4 cases; [67,68,69]after initiation of etanercep; [70]16-year-old female successful use of etanercept; [71]8 patients, successful use of infliximab in 2 cases; [72]adult, liver transplant recipient; [73]after initiation of adalimumab, histoplasmosis.	18	37
RA	[74,75]After initiation of infliximab; [76]after initiation of etanercept; [77]76-year-old man, oral prednisolone and methotrexate; [78]leflunomide; [79,80,81]63-year-old female; [21]retrospecive study 2 cases; [23]one case; [82]visceral leishmaniasis; [83]62-year-old Japanese woman successfully treated with etanercept	112	13
S-JRA	[84]Hypocomplementemia 3 cases; [22]retrospective study, [10]2 children [85]4 patients; [86,48,87]misdiagnosed as Kawasaki disease; [88]12 year old female child, fatal; [89]child after etanercept; [90,30]38 children; [91]13 children; [92,93]9 children, etanercept potentially useful for obtaining remission in children not responding to steroids and cyclosporin A; [94]13-month-old boy; [95]five children; [31]4 children; [15]Occult MAS in patients who undergo BMA; [96]7 cases in retrospective study; [31]retrospective, 18 children; [97]hepatitis A- report of 2 cases; [98,99]after initiation of etanercept; [100]successfully treated with etanercept; [101,102]successfully treated with anakinra.	23	219
Dermatomyositis	[103]Central nervous system lesions and review eight literature cases of dermatomyositis and HLH; [24]17-year-old woman, fatal dermatomyositis with anti-Mi2 antibodies; [104,105]7 years old boy, plasmapheresis; [106]platelet-specific hemophagocytosis; [107,108]60 year old male.	7	7
Kawasaki disease	[109,25]3-year-old girl with incomplete Kawasaki disease; [110]6-year-old boy; [111]retrospective study 7 cases; [112]18-month-old child, respiratory failure, fatal; [113-115]2 cases; [116,48,117]autoimmune hemolytic anemia; [118]32-month-old Japanese boy; [119]2 cases; [120]14-year-old boy; [121,122]5-year-old girl, response to gamma-globulin therapy, ischemic colitis; [123]infant of 7 weeks after clinical response to treatment, suddenly died from a myocardial infarction at 11 weeks.	17	25

Table Continued

Table II *(Continued)*. Papers describing cases of HLH in the course of rheumatic diseases.

Systemic disease	References and note	N° parer/ cases	
SSc	[26]After initiation of etanercept; [124]MPO-ANCA positive vasculitis; [21]retrospecive study 1 case; [125]33-year-old woman, etoposide; [126]32-year-old woman	5	5
Behcet disease	[27]43-year-old man, EBV	1	1
Polyarteritis nodosa	[28]73-year-old woman, EBV reactivation; [21]retrospecive study 2 cases; [31]retrospective, 2 children[127]	4	6
Ankylosing spondylitis	[128]Ankylosing spondylitis, infliximab; [129]42-year-old woman	2	2
Mixed connective tissue disease	[21]Retrospecive study 1 case;	1	1
Sarcoidosis	[21]Retrospecive study 1 case; [130,131]42-year-old Indian patient with a 7-year-history, of sarcoidosis miliary tuberculosis, steroid, fatal; [132,133]chronic steroid treatment, *Histoplasma capsulatum*	5	5
Sjögren's syndrome	[21]Retrospecive study 1 case; [134]one case; [23]one case	3	3
Wegener's granulomatosis	[29]Azathioprine, prednisone, disseminated infection with herpes simplex virus-1.	1	1
Unclassifiable disorders	[31]Retrospective, 2 children	1	2

RA = Rheumatoid arthritis; SLE = Systemic lupus erythematosus; S-JRA = Systemic juvenile arthritis; SSc = Systemic sclerosis.

tients)[21,26, 124-126], Behcet disease (one patient)[27], polyarteritis nodosa (6 patients)[21,28,31,127], ankylosing spondylitis (2 patients)[128,129], mixed connective tissue disease (one patient)[21], sarcoidosis (5 papers)[21,130-133], Sjögren's syndrome (3 patients)[21,23,134], Wegener's granulomatosis (one patient)[29], and unclassifiable disorders (two patients)[31].

Active infection was clearly reported in 16 cases of HLH: (4 CMV[40,49,50,64], 4 EBV[27,28,32,47], one HSV-1[29], one parvovirus B19[4], two hepatitis A[8], one miliary tubercolosis[12], 2 histoplasmosis[73,133], one visceral leishmaniasis[82]. An active infection triggered or was a concause of HLH in 5/94 cases of SLE, 2/37 cases of Still's disease, 1/13 cases of RA, 1/1 case of Behcet disease, 1/2 cases of polyarteritis nodosa, 2/5 of sarcoidosis, and 1/1 case of Wegener's granulomatosis.

In 20 cases HLH might have been triggered by immunosuppressive treatment of the rheumatic condition, including adalimumab[73], infliximab[74,75,128], etanercept[26,66,68,69,76,83,89,98,99], leflunomide[78], sulfasalazine[61], azathioprine[29], methotrexate[77]. Other possible triggers/cofactors were non-Hodgkin's lymphoma[41], and antimalarial drugs[65].

Of note, in 18 cases biologicals were used for HLH treatment including infliximab in three cases[53,54] etanercept in 13 cases[51,52,70,93,100] and anakinra in two cases[101,102].

Among SLE patients, HLH occurred in 2 cases after parturition, in 1 case after abortion and in 1 pregnant patient causing preeclampsia and cerebral hemorrhage[55-57].

Discussion

Secondary HLH is a rare but potentially fatal condition associated with infections, transplantation, cancers, and treatment of a variety of conditions including cancer and HIV/AIDS. Infections are the most common. Our Medline search identified 421 well-documented cases of HLH occurring in the course of rheumatic diseases.

Our review suggests that secondary HLH is more common than previously recognized, and demonstrates how HLH can complicate the course of not only S-JRA, with which it may be constitutively associated, but also of virtually any rheumatic disease. Parodi et al. proposed new diagnostic guidelines for juvenile SLE indicating that bone marrow aspiration for evidence of macrophage hemophagocytosis may be required in doubtful cases[30].

HLH should be recognized as a severe, potentially life-threatening complication of rheumatic diseases. Since HLH has a mortality rate of 8% to 22%[31], early diagnosis and immediate treatment

are crucial. In patients with systemic-onset JRA or SLE, HLH needs to be differentiated from an acute exacerbation of the underlying disease through clinical and laboratory findings. Diagnosis of HLH in systemic-onset JRA and SLE is compounded by the fact that some of the typical features, such as fever, splenomegaly, and anemia, are also seen in active systemic-onset JRA and during acute exacerbation of SLE. Other important conditions to consider in differential diagnosis include infections and adverse effects of medications.

A number of triggers have been related to the development of HLH, including viral infectious agents, in particular EBV and CMV, bacteria, parasites (leishmaniasis), fungi, and also medications, such as methotrexate, sulfasalazine, and anti-TNF-α (etanercept, infliximab)[135-142]. However, HLH may occur without any identifiable precipitating factor. Although the cause of the HLH is unknown, dysregulation of macrophage-lymphocyte interactions with subsequent increases in the levels of both T-cell-derived and macrophage- derived cytokines, particularly TNF-α, interleukin (IL)-1, IL-6, interferon gamma (IFN-γ), soluble IL-2 receptor (sIL-2R), and soluble TNF receptors (sTNFRs), could be involved in this syndrome[143]. Such dysregulation leads to an intense systemic inflammatory reaction. Our data shown that S-JRA and SLE predominated among the rheumatic disease complicated by HLH. In patients with S-JRA it was proposed that severely reduced expression of perforin on CD8 T cells and natural killer (NK) cells, abnormal granzyme B expression, and low NK cell activity are linked with increased incidence of HLH[144]. SLE is an immunologically mediated disease; therefore either an immune complex-mediated or an autoantibody-mediated mechanism could participate in the pathogenesis of MAS. Other evidence suggests that cytokines, including IL-1b, IL-2, IFN-γ, IL-6, M-CSF (macrophage colony-stimulating factor), and TNF-α, play important roles in the pathogenesis of MAS associated with SLE, systemic sclerosis with vasculitis, and Kawasaki disease[39,118,124,145].

Although an abnormal immunoregulation of T cells resulting in hypercytokinemia has been proposed to contribute to the pathogenesis of HLH, the type of cytokine involved could depend on the underlying disease. Recently, other abnormalities have been demonstrated, including extensive expression of the hemoglobin scavenger receptor (CD163) in an SLE patient with HLH and a severe IL-18/ IL-18BP imbalance in HLH secondary to other conditions. Expression of CD163 and determination of serum levels of soluble CD163 have been found to be useful clinical markers of HLH and other disorders associated with overwhelming macrophage activity[48,146] while IL-18/IL-18BP imbalance may result in Th-1 lymphocyte and macrophage activation, which escapes control by NK-cell cytotoxicity and may allow for secondary HLH in patients with underlying diseases[147,148].

Our data showed 20 cases in which HLH appeared triggered by anti-TNF-α treatment, it is a paradox, in fact as TNF-α seems to have a pivotal role in HLH and the use of inhibitors of TNF-α to treat this syndrome has been proposed[100,93] (notably, we found 18 cases in which biological were used in the treatment of HLH).

It is possible that immunosuppression induced by anti-TNF-α treatment may favor the occurrence of serious infections leading, in turn, to HLH.

Furthermore, it should stressed that the identification of hemophagocytosis in bone marrow aspirate (BMA) represents only one of 5/8 criteria needed for the diagnosis of HLH. Gupta et al[149] pointed out that the number of hemophagocytosis at initial BMA is often low and variable, confirming that a BMA lacking hemophagocytosis does not rule out the diagnosis of HLH. Furthermore, a diagnosis of primary HLH should always be excluded. In fact, with improved molecular diagnostics it is recognized that cases of adult onset HLH that had previously been considered secondary may represent a primary HLH with underlying mutation in the PFR1 gene[150,151].

Treatment of HLH in patients with rheumatic diseases has not been standardized yet, but it commonly includes a variety of agents such as corticosteroids, cyclosporine A, intravenous immunoglobulins, etoposide, cyclophosphamide, anti-TNF-α, methotrexate, G-CSF (granulocyte colony-stimulating factor), and in some cases plasmaphereis. Infectious causes should be treated promptly along with administering supportive care. Treatment should be started without delay, yet it should be kept in mind that the use of immunosuppression may further delay the diagnosis and definitive treatment

Conclusions

HLH occurring in the course of rheumatic diseases is an important and often underdiagnosed clinical entity, which can affect prognosis. Physicians must keep the symptoms of HLH in mind,

particularly because it is difficult to distinguish HLH symptoms from those of several rheumatic disease. A triggering infective cause should be always accurately searched and antinfective treatment started in the case of active infection.

References

1) Loza E, Abasolo L, Jover JA, Carmona L. Burden of disease across chronic diseases: a health survey that measured prevalence, function, and quality of life. J Rheumatol 2008; 35: 159-165.
2) Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Res Ther 2009; 11: 229.
3) Arico M, Janka G, Fischer A, Henter JI, Blanche S, Elinder G, Martinetti M, Rusca MP. Hemophagocytic lymphohistiocytosis. Report of 122 children from the International Registry. FHL Study Group of the Histiocyte Society. Leukemia 1996; 10: 197-203.
4) Janka GE. Familial hemophagocytic lymphohistiocytosis. Eur J Pediatr 1983; 140: 221-230.
5) Gupta S, Weitzman S. Primary and secondary hemophagocytic lymphohistiocytosis: clinical features, pathogenesis and therapy. Expert Rev Clin Immunol 2010; 6: 137-154.
6) Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007; 48: 124-131.
7) Henter JI. Biology and treatment of familial hemophagocytic lymphohistiocytosis: importance of perforin in lymphocyte-mediated cytotoxicity and triggering of apoptosis. Med Pediatr Oncol 2002; 38: 305-309.
8) Komp DM, Buckley PJ, McNamara J, van Hoff J. Soluble interleukin-2 receptor in hemophagocytic histiocytoses: searching for markers of disease activity. Pediatr Hematol Oncol 1989; 6: 253-264.
9) Biondo C, Malara A, Costa A, Signorino G, Cardile F, Midiri A, Galbo R, Papasergi S, Domina M, Pugliese M, Teti G, Mancuso G, Beninati C. Recognition of fungal RNA by TLR7 has a nonredundant role in host defense against experimental candidiasis. Eur J Immunol 2012; doi: 10.1002/eji.201242532.
10) Cardaci A, Papasergi S, Midiri A, Mancuso G, Domina M, Cariccio VL, Mandanici F, Galbo R, Lo Passo C, Pernice I, Donato P, Ricci S, Biondo C, Teti G, Felici F, Beninati C. Protective activity of Streptococcus pneumoniae Spr1875 protein fragments identified using a phage displayed genomic library. PLoS One 2012; 7: e36588.
11) Costa A, Gupta R, Signorino G, Malara A, Cardile F, Biondo C, Midiri A, Galbo R, Trieu-Cuot P, Papasergi S, Teti G, Henneke P, Mancuso G, Golenbock DT, Beninati C. Activation of the NLRP3 inflammasome by group B streptococci. J Immunol 2011; 188: 1953-1960.
12) Biondo C, Signorino G, Costa A, Midiri A, Gerace E, Galbo R, Bellantoni A, Malara A, Beninati C, Teti G, Mancuso G. Recognition of yeast nucleic acids triggers a host-protective type I interferon response. Eur J Immunol 2011; 41: 1969-1979.
13) Risdall RJ, Brunning RD, Hernandez JI, Gordon DH. Bacteria-associated hemophagocytic syndrome. Cancer 1984; 54: 2968-2972.
14) Janka G, Imashuku S, Elinder G, Schneider M, Henter JI. Infection- and malignancy-associated hemophagocytic syndromes. Secondary hemophagocytic lymphohistiocytosis. Hematol Oncol Clin North Am 1998; 12: 435-444.
15) Behrens EM, Beukelman T, Paessler M, Cron RQ. Occult macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis. J Rheumatol 2007; 34: 1133-1138.
16) Vastert SJ, van Wijk R, D'Urbano LE, de Vooght KM, de Jager W, Ravelli A, Magni-Manzoni S, Insalaco A, Cortis E, van Solinge WW, Prakken BJ, Wulffraat NM, de Benedetti F, Kuis W. Mutations in the perforin gene can be linked to macrophage activation syndrome in patients with systemic onset juvenile idiopathic arthritis. Rheumatology (Oxford) 2010; 49: 441-449.
17) Yanagimachi M, Goto H, Miyamae T, Kadota K, Imagawa T, Mori M, Sato H, Yanagisawa R, Kaneko T, Morita S, Ishii E, Yokota S. Association of IRF5 polymorphisms with susceptibility to hemophagocytic lymphohistiocytosis in children. J Clin Immunol 2011; 31: 946-951.
18) Ravelli A, Grom AA, Behrens EM, Cron RQ. Macrophage activation syndrome as part of systemic juvenile idiopathic arthritis: diagnosis, genetics, pathophysiology and treatment. Genes Immun 2012; 13: 289-298.
19) Lambotte O, Khellaf M, Harmouche H, Bader-Meunier B, Manceron V, Goujard C, Amoura Z, Godeau B, Piette JC, Delfraissy JF. Characteristics and long-term outcome of 15 episodes of systemic lupus erythematosus-associated hemophagocytic syndrome. Medicine (Baltimore) 2006; 85: 169-182.
20) Kim JM, Kwok SK, Ju JH, Kim HY, Park SH. Reactive hemophagocytic syndrome in adult Korean patients with systemic lupus erythematosus: a case-control study and literature review. J Rheumatol 2012; 39: 86-93.
21) Dhote R, Simon J, Papo T, Detournay B, Sailler L, Andre MH, Dupond JL, Larroche C, Piette AM, Mechenstock D, Ziza JM, Arlaud J, Labussiere AS, Desvaux A, Baty V, Blanche P, Schaeffer A, Piette JC, Guillevin L, Boissonnas A, Christoforov B. Reactive hemophagocytic syndrome in adult systemic disease: report of twenty-six cases and literature review. Arthritis Rheum 2003; 49: 633-639.
22) Bennett TD, Fluchel M, Hersh AO, Hayward KN, Hersh AL, Brogan TV, Srivastava R, Stone BL, Korgenski EK, Mundorff MB, Casper TC, Bratton SL.

Macrophage activation syndrome in children with systemic lupus erythematosus and juvenile idiopathic arthritis. Arthritis Rheum 2012.

23) Sun XH, Zheng WJ, Zhang W, Zhao Y. [A clinical analysis of hemophagocytic syndrome in autoimmune diseases]. Zhonghua Nei Ke Za Zhi; 49: 836-840.

24) 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: 1157-1158.

25) Suresh N, Sankar J. Macrophage activation syndrome: a rare complication of incomplete Kawasaki disease. Ann Trop Paediatr 2010; 30: 61-64.

26) Sterba G, Sterba Y, Stempel C, Blank J, Azor E, Gomez L. Macrophage activation syndrome induced by etanercept in a patient with systemic sclerosis. Isr Med Assoc J 2010; 12: 443-445.

27) Lee SH, Kim SD, Kim SH, Kim HR, Oh EJ, Yoon CH, Kim HY, Park SH. EBV-associated haemophagocytic syndrome in a patient with Behcet's disease. Scand J Rheumatol 2005; 34: 320-323.

28) Hayakawa I, Shirasaki F, Ikeda H, Oishi N, Hasegawa M, Sato S, Takehara K. Reactive hemophagocytic syndrome in a patient with polyarteritis nodosa associated with Epstein-Barr virus reactivation. Rheumatol Int 2006; 26: 573-576.

29) Cusini A, Gunthard HF, Stussi G, Schwarz U, Fehr T, Grueter E, Meerbach A, Bossart W, Schaer DJ, Rudiger A. Hemophagocytic syndrome caused by primary herpes simplex virus 1 infection: report of a first case. Infection 2010; 38: 423-426.

30) Parodi A, Davi S, Pringe AB, Pistorio A, Ruperto N, Magni-Manzoni S, Miettunen P, Bader-Meunier B, Espada G, Sterba G, Ozen S, Wright D, Magalhaes CS, Khubchandani R, Michels H, Woo P, Iglesias A, Guseinova D, Bracaglia C, Hayward K, Wouters C, Grom A, Vivarelli M, Fischer A, Breda L, Martini A, Ravelli A. Macrophage activation syndrome in juvenile systemic lupus erythematosus: a multinational multicenter study of thirty-eight patients. Arthritis Rheum 2009; 60: 3388-3399.

31) Stephan JL, Kone-Paut I, Galambrun C, Mouy R, Bader-Meunier B, Prieur AM. Reactive haemophagocytic syndrome in children with inflammatory disorders. A retrospective study of 24 patients. Rheumatology (Oxford) 2001; 40: 1285-1292.

32) Moon SJ, Kwok SK, Park KS, Kim WU, Park SH, Kim HY. Simultaneous presentation of hemophagocytic syndrome and mesenteric vasculitis in a patient with systemic lupus erythematosus. Mod Rheumatol 2011; 21: 330-333.

33) Botelho C, Ferrer F, Francisco L, Maia P, Mendes T, Carreira A. Acute lupus hemophagocytic syndrome: report of a case. Nefrologia 2009; 30: 247-251.

34) Maeshima E, Kobayashi T, Mune M, Yukawa S. Systemic lupus erythematosus with haemophagocytosis and severe liver disorder. Ann Rheum Dis 2002; 61: 753-754.

35) Nawata M, Suzuki J, Ikeda K, Ando S, Koike M, Sekigawa I, Iida N, Wada R, Matsumoto M, Oshimi K, Hashimoto H. Haemophagocytic syndrome in a systemic lupus erythematosus patient with antiphospholipid antibodies. Rheumatology (Oxford) 2001; 40: 828-829.

36) Carvalheiras G, Anjo D, Mendonca T, Vasconcelos C, Farinha F. Hemophagocytic syndrome as one of the main primary manifestations in acute systemic lupus erythematosus--case report and literature review. Lupus 2010; 19: 756-761.

37) Taki H, Shinoda K, Hounoki H, Ogawa R, Hayashi R, Sugiyama E, Tobe K. Presenting manifestations of hemophagocytic syndrome in a male patient with systemic lupus erythematosus. Rheumatol Int 2010; 30: 387-388.

38) Koseto M, Murakami A, Tatekawa T, Fujii T, Suzuki T. [Hemophagocytic syndrome in a patient with systemic lupus erythematosus]. Nihon Naika Gakkai Zasshi 2001; 90: 696-698.

39) Takahashi K, Kumakura S, Ishikura H, Murakawa Y, Yamauchi Y, Kobayashi S. Reactive hemophagocytosis in systemic lupus erythematosus. Intern Med 1998; 37: 550-553.

40) Tanaka Y, Seo R, Nagai Y, Mori M, Togami K, Fujita H, Kurata M, Matsushita A, Maeda A, Nagai K, Kotani H, Takahashi T. Systemic lupus erythematosus complicated by cytomegalovirus-induced hemophagocytic syndrome and pneumonia. Nihon Rinsho Meneki Gakkai Kaishi 2008; 31: 71-75.

41) Jeremic I, Dordevic-Kontic S, Nikolic M, Sefik-Bukilica M, Vujasinovic-Stupar N, Bonaci-Nikolic B. Systemic lupus erythematosus progressing to non-Hodgkin's lymphoma complicated by fatal hemophagocytic syndrome: case report. Acta Dermatovenerol Croat 2012; 20: 21-26.

42) McCann LJ, Hasson N, Pilkington CA. Macrophage activation syndrome as an early presentation of Lupus. J Rheumatol 2006; 33: 438-440.

43) Okada M, Suzuki K, Hidaka T, Shinohara T, Katahara-da K, Matsumoto M, Takada K, Ohsuzu F. Hemophagocytic syndrome in systemic lupus erythematosus. Intern Med 2001; 40: 1263-1264.

44) Sakai H, Otsubo S, Miura T, Iizuka H. Hemophagocytic syndrome presenting with a facial erythema in a patient with systemic lupus erythematosus. J Am Acad Dermatol 2007; 57: S111-114.

45) Romanou V, Hatzinikolaou P, Mavragani KI, Meletis J, Vaiopoulos G. Lupus erythematosus complicated by hemophagocytic syndrome. J Clin Rheumatol 2006; 12: 301-303.

46) Hagiwara K, Sawanobori M, Nakagawa Y, Sato T, Akiyama O, Takemura T. Reactive hemophagocytic syndrome in a case of systemic lupus erythematosus that was diagnosed by detection of hemophagocytosing macrophages in peripheral blood smears. Mod Rheumatol 2006; 16: 169-171.

47) Isome M, Suzuki J, Takahashi A, Murai H, Nozawa R, Suzuki S, Kawasaki Y, Suzuki H. Epstein-Barr virus-associated hemophagocytic syndrome in a patient with lupus nephritis. Pediatr Nephrol 2005; 20: 226-228.

48) Avcin T, Tse SM, Schneider R, Ngan B, Silverman ED. Macrophage activation syndrome as the presenting manifestation of rheumatic diseases in childhood. J Pediatr 2006; 148: 683-686.

49) Sakamoto O, Ando M, Yoshimatsu S, Kohrogi H, Suga M. Systemic lupus erythematosus complicated by cytomegalovirus-induced hemophagocytic syndrome and colitis. Intern Med 2002; 41: 151-155.

50) Eguchi K. Systemic lupus erythematosus complicated by cytomegalovirus-induced hemophagocytic syndrome and colitis. Intern Med 2002; 41: 77-78.

51) Kikuchi H, Yamamoto T, Asako K, Takayama M, Shirasaki R, Ono Y. Etanercept for the treatment of intractable hemophagocytic syndrome with systemic lupus erythematosus. Mod Rheumatol 2011; 22: 308-311.

52) Takahashi N, Naniwa T, Banno S. Successful use of etanercept in the treatment of acute lupus hemophagocytic syndrome. Mod Rheumatol 2008; 18: 72-75.

53) Ideguchi H, Ohno S, Takase K, Hattori H, Kirino Y, Takeno M, Ishigatsubo Y. Successful treatment of refractory lupus-associated haemophagocytic lymphohistiocytosis with infliximab. Rheumatology (Oxford) 2007; 46: 1621-1622.

54) Henzan T, Nagafuji K, Tsukamoto H, Miyamoto T, Gondo H, Imashuku S, Harada M. Success with infliximab in treating refractory hemophagocytic lymphohistiocytosis. Am J Hematol 2006; 81: 59-61.

55) Perard L, Costedoat-Chalumeau N, Limal N, Hot A, Cohen J, Vauthier-Brouzes D, Nieszkowska A, Belmatoug N, Piette JC. Hemophagocytic syndrome in a pregnant patient with systemic lupus erythematosus, complicated with preeclampsia and cerebral hemorrhage. Ann Hematol 2007; 86: 541-544.

56) Qian J, Yang CD. Hemophagocytic syndrome as one of main manifestations in untreated systemic lupus erythematosus: two case reports and literature review. Clin Rheumatol 2007; 26: 807-810.

57) Yoshida S, Takeuchi T, Itami Y, Hata K, Watanabe K, Shoda T, Kotani T, Makino S, Hanafusa T. Hemophagocytic syndrome as primary manifestation in a patient with systemic lupus erythematosus after parturition. Nihon Rinsho Meneki Gakkai Kaishi 2009; 32: 66-70.

58) Fujii K, Kitamura Y, Osugi Y, Koyama Y, Ota T. A case of adult-onset Still's disease complicated by hemophagocytic syndrome and interstitial pneumonia with pneumomediastinum/recurrent pneumothorax. Int J Rheum Dis 2012; 15: e60-62.

59) Cornet AD, Thielen N, Kramer MH, Nanayakkara PW, Kooter AJ. [Adult-onset Still's disease and haemophagocytic syndrome]. Ned Tijdschr Geneeskd 2010; 154: A2528.

60) Lopez-Sanchez M, Rubio-Lopez I, Obeso-Gonzalez T, Teja-Barbero JL, Santidrian-Miguel JP, Peiro-Callizo E. [Multi-organ failure as first clinical sign of macrophage activation syndrome in childhood Still's disease]. An Pediatr (Barc) 2010; 73: 194-198.

61) Perez-De Pedro I, Miranda-Candon I, Camps-Garcia MT, Gomez-Huelgas R. [Hemophagocytic syndrome in adult Still disease after initiation of sulfasalazine]. Rev Clin Esp 2010; 210: 251-252.

62) Bodemer C, Stephan JL, Prieur AM, Teillac D, Cloup M, de Prost Y. [Hemophagocytic syndrome. 2 cases in children with Still's disease]. Ann Dermatol Venereol 1991; 118: 810-812.

63) Yeh HM, Liu MF, Chang KK, Liu SM, Chen CH. Adult-onset Still's disease complicated with hemophagocytic syndrome. J Formos Med Assoc 2010; 109: 85-88.

64) Amenomori M, Migita K, Miyashita T, Yoshida S, Ito M, Eguchi K, Ezaki H. Cytomegalovirus-associated hemophagocytic syndrome in a patient with adult onset Still's disease. Clin Exp Rheumatol 2005; 23: 100-102.

65) Pamuk ON, Pamuk GE, Usta U, Cakir N. Hemophagocytic syndrome in one patient with adult-onset Still's disease. Presentation with febrile neutropenia. Clin Rheumatol 2007; 26: 797-800.

66) Arlet JB, Le TH, Marinho A, Amoura Z, Wechsler B, Papo T, Piette JC. Reactive haemophagocytic syndrome in adult-onset Still's disease: a report of six patients and a review of the literature. Ann Rheum Dis 2006; 65: 1596-1601.

67) Mehta BM, Hashkes PJ, Avery R, Deal CL. A 21-year-old man with Still's disease with fever, rash, and pancytopenia. Arthritis Care Res (Hoboken) 2010; 62: 575-579.

68) Gianella S, Schaer DJ, Schwarz U, Kurrer M, Heppner FL, Fehr J, Seebach JD. Retinal microangiopathy and rapidly fatal cerebral edema in a patient with adult-onset Still's disease and concurrent macrophage activation syndrome. Am J Hematol 2008; 83: 424-427.

69) Stern A, Riley R, Buckley L. Worsening of macrophage activation syndrome in a patient with adult onset Still's disease after initiation of etanercept therapy. J Clin Rheumatol 2001; 7: 252-256.

70) Maeshima K, Ishii K, Iwakura M, Akamine M, Hamasaki H, Abe I, Haranaka M, Tatsukawa H, Yoshimatsu H. Adult-onset Still's disease with macrophage activation syndrome successfully treated with a combination of methotrexate and etanercept. Mod Rheumatol 2012; 22: 137-141.

71) Hot A, Toh ML, Coppere B, Perard L, Madoux MH, Mausservey C, Desmurs-Clavel H, Ffrench M, Ninet J. Reactive hemophagocytic syndrome in adult-onset Still disease: clinical features and long-term outcome: a case-control study of 8 patients. Medicine (Baltimore) 2010; 89: 37-46.

72) Satapathy SK, Isabel Fiel M, Del Rio Martin J, Aloman C, Schiano TD. Hemophagocytic syndrome occurring in an adult liver transplant recipient having Still's disease. Hepatol Int 2010; 5: 597-602.

73) Agarwal S, Moodley J, Ajani Goel G, Theil KS, Mahmood SS, Lang RS. A rare trigger for macrophage activation syndrome. Rheumatol Int 2011; 31: 405-407.

74) Oda Y, Urushidani Y, Ooi S, Endoh A, Nakamura R, Adachi K, Fukushima H. Hemophagocytic lymphohistiocytosis in a rheumatoid arthritis patient treated with infliximab. Intern Med 2012; 51: 655-657.

75) Aouba A, De Bandt M, Aslangul E, Atkhen N, Patri B. Haemophagocytic syndrome in a rheumatoid arthritis patient treated with infliximab. Rheumatology (Oxford) 2003; 42: 800-802.

76) Sandhu C, Chesney A, Piliotis E, Buckstein R, Koren S. Macrophage activation syndrome after etanercept treatment. J Rheumatol 2007; 34: 241-242.

77) Tsuboi H, Iwata H, Nampei A, Matsushita M, Shi K. Hemophagocytic syndrome in a patient with rheumatoid arthritis. Mod Rheumatol 2011; 21: 532-535.

78) Ricci M, Rossi P, De Marco G, Varisco V, Marchesoni A. Macrophage activation syndrome after leflunomide treatment in an adult rheumatoid arthritis patient. Rheumatology (Oxford) 2010; 49: 2001.

79) Niang A, Diallo S, Ka MM, Pouye A, Diop S, Ndongo S, Diop TM. [Hemophagocytic syndrome complicating adult's seropositive rheumatoid arthritis]. Rev Med Interne 2004; 25: 826-828.

80) Negishi M, Kasama T, Iwabuchi H, Kanemitsu H, Ide H. Autoimmune-associated haemophagocytic syndrome in a patient with rheumatoid arthritis. Clin Rheumatol 2002; 21: 87-88.

81) Onishi R, Namiuchi S. Hemophagocytic syndrome in a patient with rheumatoid arthritis. Intern Med 1994; 33: 607-611.

82) Molto A, Mateo L, Lloveras N, Olive A, Minguez S. Visceral leishmaniasis and macrophagic activation syndrome in a patient with rheumatoid arthritis under treatment with adalimumab. Joint Bone Spine 2010; 77: 271-273.

83) Araki D, Fujii H, Matsumura M, Yamagishi M, Yachie A, Kawano M. Etanercept-induced lupus accompanied by hemophagocytic syndrome. Intern Med 2011; 50: 1843-1848.

84) Gorelik M, Torok KS, Kietz DA, Hirsch R. Hypocomplementemia associated with macrophage activation syndrome in systemic juvenile idiopathic arthritis and adult onset still's disease: 3 cases. J Rheumatol 2011; 38: 396-397.

85) Singh S, Chandrakasan S, Ahluwalia J, Suri D, Rawat A, Ahmed N, Das R, Sachdeva MU, Varma N. Macrophage activation syndrome in children with systemic onset juvenile idiopathic arthritis: clinical experience from northwest India. Rheumatol Int 2012; 32: 881-886.

86) Tristano AG. Macrophage activation syndrome associated with systemic onset juvenile rheumatoid arthritis. South Med J 2006; 99: 786-787.

87) Kumar S, Vaidyanathan B, Gayathri S, Rajam L. Systemic onset juvenile idiopathic arthritis with macrophage activation syndrome misdiagnosed as Kawasaki disease: case report and literature review. Rheumatol Int 2010.

88) Juneja M, Jain R, Mishra D. Macrophage activation syndrome in an inadequately treated patient with systemic onset juvenile idiopathic arthritis. Kathmandu Univ Med J (KUMJ) 2009; 7: 411-413.

89) Sawar H, Espinoza LR, Gedalia A. Macrophage activation syndrome and etanercept in children with systemic juvenile rheumatoid arthritis. J Rheumatol 2004; 31: 623; author reply 623-624.

90) Cuende E, Vesga JC, Perez LB, Ardanaz MT, Guinea J. Macrophage activation syndrome as the initial manifestation of systemic onset juvenile idiopathic arthritis. Clin Exp Rheumatol 2001; 19: 764-765.

91) Zeng HS, Xiong XY, Wei YD, Wang HW, Luo XP. Macrophage activation syndrome in 13 children with systemic-onset juvenile idiopathic arthritis. World J Pediatr 2008; 4: 97-101.

92) Zhao Y, Cao LF. [A case report of macrophage activation syndrome complicated by systemic onset juvenile idiopathic arthritis]. Zhongguo Dang Dai Er Ke Za Zhi 2007; 9: 610.

93) Cortis E, Insalaco A. Macrophage activation syndrome in juvenile idiopathic arthritis. Acta Paediatr Suppl 2006; 95: 38-41.

94) Hur M, Kim YC, Lee KM, Kim KN. Macrophage activation syndrome in a child with systemic juvenile rheumatoid arthritis. J Korean Med Sci 2005; 20: 695-698.

95) Kounami S, Yoshiyama M, Nakayama K, Okuda M, Okuda S, Aoyagi N, Yoshikawa N. Macrophage activation syndrome in children with systemic-onset juvenile chronic arthritis. Acta Haematol 2005; 113: 124-129.

96) Silva CA, Silva CH, Robazzi TC, Lotito AP, Mendroni Junior A, Jacob CM, Kiss MH. [Macrophage activation syndrome associated with systemic juvenile idiopathic arthritis]. J Pediatr (Rio J) 2004; 80: 517-522.

97) Russo RA, Rosenzweig SD, Katsicas MM. Hepatitis A-associated macrophage activation syndrome in children with systemic juvenile idiopathic arthritis: report of 2 cases. J Rheumatol 2008; 35: 166-168.

98) Nadia EA, Carvalho JF, Bonfa E, Lotito AP, Silva CA. Macrophage activation syndrome associated with etanercept in a child with systemic onset juvenile idiopathic arthritis. Isr Med Assoc J 2009; 11: 635-636.

99) Ramanan AV, Schneider R. Macrophage activation syndrome following initiation of etanercept in a child with systemic onset juvenile rheumatoid arthritis. J Rheumatol 2003; 30: 401-403.

100) Prahalad S, Bove KE, Dickens D, Lovell DJ, Grom AA. Etanercept in the treatment of macrophage activation syndrome. J Rheumatol 2001; 28: 2120-2124.

101) Bruck N, Suttorp M, Kabus M, Heubner G, Gahr M, Pessler F. Rapid and sustained remission of systemic juvenile idiopathic arthritis-associated macrophage activation syndrome through treatment with anakinra and corticosteroids. J Clin Rheumatol 2011; 17: 23-27.

102) Kelly A, Ramanan AV. A case of macrophage activation syndrome successfully treated with anakinra. Nat Clin Pract Rheumatol 2008; 4: 615-620.

103) Yamashita H, Matsuki Y, Shimizu A, Mochizuki M, Takahashi Y, Kano T, Mimori A. Hemophagocytic lymphohistiocytosis complicated by central nervous system lesions in a patient with dermatomyositis: a case presentation and literature review. Mod Rheumatol 2012.

104) Yasuda S, Tsutsumi A, Nakabayashi T, Horita T, Ichikawa K, Ieko M, Koike T. Haemophagocytic syndrome in a patient with dermatomyositis. Br J Rheumatol 1998; 37: 1357-1358.

105) Bustos BR, Carrasco AC, Toledo RC. [Plasmapheresis for macrophage activation syndrome and multiorgan failure as first presentation of juvenile dermatomyositis]. An Pediatr (Barc); 77: 47-50.

106) 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: 617-619.

107) Yajima N, Wakabayashi K, Odai T, Isozaki T, Matsunawa M, Miwa Y, Negishi M, Ide H, Kasama T. Clinical features of hemophagocytic syndrome in patients with dermatomyositis. J Rheumatol 2008; 35: 1838-1841.

108) Sugihara T, Imai Y, Sakurai T. [Case of hemophagocytic syndrome associated with active dermatomyositis]. Nihon Rinsho Meneki Gakkai Kaishi 2002; 25: 344-350.

109) Ning BT, Zhang CM, Tang YM. [Hemophagocytic lymphohistiocytosis in a patient with Kawasaki disease]. Zhonghua Er Ke Za Zhi 2010; 48: 543-544.

110) al-Eid W, al-Jefri A, Bahabri S, al-Mayouf S. Hemophagocytosis complicating Kawasaki disease. Pediatr Hematol Oncol 2000; 17: 323-329.

111) Latino GA, Manlhiot C, Yeung RS, Chahal N, McCrindle BW. Macrophage activation syndrome in the acute phase of Kawasaki disease. J Pediatr Hematol Oncol 2010; 32: 527-531.

112) Chen Y, Shang S, Zhang C, Liu T, Yang Z, Tang Y. Hemophagocytic lymphohistiocytosis at initiation of kawasaki disease and their differential diagnosis. Pediatr Hematol Oncol 2010; 27: 244-249.

113) Cummings C, McCarthy P, van Hoff J, Porter G, Jr. Kawasaki disease associated with reactive hemophagocytic lymphohistiocytosis. Pediatr Infect Dis J 2008; 27: 1116-1118.

114) Hendricks M, Pillay S, Davidson A, De Decker R, Lawrenson J. Kawasaki disease preceding haemophagocytic lymphohistiocytosis: challenges for developing world practitioners. Pediatr Blood Cancer; 54: 1023-1025.

115) Hu XF, Wang HW, Shi H. [Macrophage activation syndrome in 2 cases with Kawasaki disease: clinical analysis and review of literature]. Zhonghua Er Ke Za Zhi 2006; 44: 833-835.

116) Kaneko K, Takahashi K, Fujiwara S, Maruyama T, Obinata K. Kawasaki disease followed by haemophagocytic syndrome. Eur J Pediatr 1998; 157: 610-611.

117) Liu RH, Liu HL. [Kawasaki disease complicated by autoimmune hemolytic anemia and macrophage activation syndrome: a case report]. Zhongguo Dang Dai Er Ke Za Zhi 2009; 11: 778-779.

118) Ohga S, Ooshima A, Fukushige J, Ueda K. Histiocytic haemophagocytosis in a patient with Kawasaki disease: changes in the hypercytokinaemic state. Eur J Pediatr 1995; 154: 539-541.

119) Palazzi DL, McClain KL, Kaplan SL. Hemophagocytic syndrome after Kawasaki disease. Pediatr Infect Dis J 2003; 22: 663-666.

120) Servel AC, Vincenti M, Darras JP, Lalande M, Rodiere M, Filleron A. [Intravenous immunoglobulin-resistant Kawasaki disease with hemophagocytosis]. Arch Pediatr 2012; 19: 741-744.

121) Simonini G, Pagnini I, Innocenti L, Calabri GB, De Martino M, Cimaz R. Macrophage activation syndrome/Hemophagocytic Lymphohistiocytosis and Kawasaki disease. Pediatr Blood Cancer; 55: 592.

122) Thabet F, Bellara I, Tabarki B, Kchaou H, Selmi H, Yacoub M, Essoussi AS. [Ischemic colitis and hemophagocytosis complicating Kawasaki disease]. Arch Pediatr 2004; 11: 226-228.

123) Titze U, Janka G, Schneider EM, Prall F, Haffner D, Classen CF. Hemophagocytic lymphohistiocytosis and Kawasaki disease: combined manifestation and differential diagnosis. Pediatr Blood Cancer 2009; 53: 493-495.

124) Kumakura S, Ishikura H, Kondo M, Murakawa Y, Kobayashi S. Hemophagocytosis associated with MPO-ANCA positive vasculitis in systemic sclerosis. Clin Exp Rheumatol 2002; 20: 411-414.

125) Katsumata Y, Okamoto H, Harigai M, Ota S, Uesato M, Tochimoto A, Kawaguchi Y, Terai C, Hara M, Kamatani N. [Etoposide ameliorated refractory hemophagocytic syndrome in a patient with systemic sclerosis]. Ryumachi 2002; 42: 820-826.

126) Tochimoto A, Nishimagi E, Kawaguchi Y, Kobashigawa T, Okamoto H, Harigai M, Terai C, Hara M, Kamatani N. [A case of recurrent hemophagocytic syndrome complicated with systemic sclerosis: relationship between disease activity and serum level of IL-18]. Ryumachi 2001; 41: 659-664.

127) Harrold LR, Liu NY. Polyarteritis nodosa presenting as pancytopenia: case report and review of the literature. Rheumatol Int 2008; 28: 1049-1051.

128) Troncoso Marino A, Campelo Sanchez E, Martinez Lopez de Castro N, Inaraja Bobo MT. Haemophagocytic syndrome and paradoxical reaction to tuberculostatics after treatment with infliximab. Pharm World Sci 2010; 32: 117-119.

129) Lou YJ, Jin J, Mai WY. Ankylosing spondylitis presenting with macrophage activation syndrome. Clin Rheumatol 2007; 26: 1929-1930.

130) Balduini CL, Noris P, Loni C, Aiosa C. Hemophagocytic syndrome responding to high-dose gammaglobulin as presenting feature of sarcoidosis. Am J Hematol 1997; 54: 88-89.

131) Lam KY, Ng WF, Chan AC. Miliary tuberculosis with splenic rupture: a fatal case with hemophagocytic syndrome and possible association with long standing sarcoidosis. Pathology 1994; 26: 493-496.

132) Okabe T, Shah G, Mendoza V, Hirani A, Baram M, Marik P. What intensivists need to know about hemophagocytic syndrome: an underrecognized cause of death in adult intensive care units. J Intensive Care Med; 27: 58-64.

133) Phillips J, Staszewski H, Garrison M. Successful treatment of secondary hemophagocytic lymphohistiocytosis in a patient with disseminated histoplasmosis. Hematology 2008; 13: 282-285.

134) Ben Dhaou Hmaidi B, Derbali F, Boussema F, Ketari Jamoussi S, Baili L, Kochbati S, Cherif O, Rokbani L. [Hemophagocytic syndrome: report of 4 cases]. Tunis Med 2011; 89: 70-75.

135) Cascio A, Iaria M, Iaria C. Leishmaniasis and biologic therapies for rheumatologic diseases. Semin Arthritis Rheum 2010; 40: e3-5.

136) Cascio A, Iaria C, Ruggeri P, Fries W. Cytomegalovirus pneumonia in patients with inflammatory bowel disease: a systematic review. Int J Infect Dis 2012; 16: e474-479.

137) Cascio A, Iaria C, Antinori S. Visceral leishmaniasis as a cause of anemia in HIV-infected patients. Clin Infect Dis 2004; 39: 1088-1089.

138) Cascio A, Giordano S, Dones P, Venezia S, Iaria C, Zino O. Haemophagocytic syndrome and rickettsial diseases. J Med Microbiol 2011; 60: 537-542.

139) Cascio A, Todaro G, Bonina L, Iaria C. Please, do not forget secondary hemophagocytic lymphohistiocytosis in HIV-infected patients. Int J Infect Dis 2011; 15: e885-886.

140) David A, Iaria C, Giordano S, Iaria M, Cascio A. Secondary hemophagocytic lymphohistiocytosis: forget me not! Transpl Infect Dis 2012.

141) Iaria C, Leonardi MS, Buda A, Toro ML, Cascio A. Measles and secondary hemophagocytic lymphohistiocytosis. Emerg Infect Dis 2012; 18: 1529a-1529.

142) Pitini V, Cascio A, Arrigo C, Altavilla G. Visceral leishmaniasis after alemtuzumab in a patient with chronic lymphocytic leukaemia. Br J Haematol 2012; 156: 1.

143) Osugi Y, Hara J, Tagawa S, Takai K, Hosoi G, Matsuda Y, Ohta H, Fujisaki H, Kobayashi M, Sakata N, Kawa-Ha K, Okada S, Tawa A. Cytokine production regulating Th1 and Th2 cytokines in hemophagocytic lymphohistiocytosis. Blood 1997; 89: 4100-4103.

144) Grom AA, Villanueva J, Lee S, Goldmuntz EA, Passo MH, Filipovich A. Natural killer cell dysfunction in patients with systemic-onset juvenile rheumatoid arthritis and macrophage activation syndrome. J Pediatr 2003; 142: 292-296.

145) Kumakura S, Ishikura H, Munemasa S, Adachi T, Murakawa Y, Kobayashi S. Adult onset Still's disease associated hemophagocytosis. J Rheumatol 1997; 24: 1645-1648.

146) Schaer DJ, Schleiffenbaum B, Kurrer M, Imhof A, Bachli E, Fehr J, Moller HJ, Moestrup SK, Schaffner A. Soluble hemoglobin-haptoglobin scavenger receptor CD163 as a lineage-specific marker in the reactive hemophagocytic syndrome. Eur J Haematol 2005; 74: 6-10.

147) Mazodier K, Marin V, Novick D, Farnarier C, Robitail S, Schleinitz N, Veit V, Paul P, Rubinstein M, Dinarello CA, Harle JR, Kaplanski G. Severe imbalance of IL-18/IL-18BP in patients with secondary hemophagocytic syndrome. Blood 2005; 106: 3483-3489.

148) Henter JI, Tondini C, Pritchard J. Histiocyte disorders. Crit Rev Oncol Hematol 2004; 50: 157-174.

149) Gupta A, Tyrrell P, Valani R, Benseler S, Weitzman S, Abdelhaleem M. The role of the initial bone marrow aspirate in the diagnosis of hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2008; 51: 402-404.

150) Freeman HR, Ramanan AV. Review of haemophagocytic lymphohistiocytosis. Arch Dis Child 2011; 96: 688-693.

151) Nagafuji K, Nonami A, Kumano T, Kikushige Y, Yoshimoto G, Takenaka K, Shimoda K, Ohga S, Yasukawa M, Horiuchi H, Ishii E, Harada M. Perforin gene mutations in adult-onset hemophagocytic lymphohistiocytosis. Haematologica 2007; 92: 978-981.