Abstract. – BACKGROUND: Hemophagocytic lymphohistiocytosis (HLH), is a potentially fatal hyperinflammatory syndrome characterized by 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, dermatomyositis, polyarthritis nodosa, Henoch-Schönlein, serum sickness, Wegener’s granulomatosis, giant cell 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 Behçet 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.
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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. 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.

Secondary HLH, called also macrophage activation syndrome (MAS), may develop at any age and can occur during systemic infection, immunodeficiency or malignancy. 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%. Moreover, in patients with sJIA, several mutations possibly related to HLH have been recently reported. 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.

In addition, in recent years this syndrome has been increasingly reported in patients with juvenile systemic lupus erythematosus (SLE), Still’s disease and other rheumatic disorders. Because HLH is a serious condition that can follow a rapidly fatal course, its prompt recognition is imperative. The purpose of this systematic review is to draw attention on this severe syndrome that may often go undiagnosed in patients 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, Behcet’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 rheumatologic diseases who had microscopic signs of haemophagocytosis and/or fulfilled the diagnostic criteria of Study Group of the Histiocyte Society.

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**Table 1.** HLH 2004 Diagnostic criteria (modified from ref.5).  

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
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<tbody>
<tr>
<td>1. Molecular diagnosis consistent with HLH</td>
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<tr>
<td>2. Diagnostic criteria for HLH are fulfilled (five out of the eight criteria below):</td>
<td>Fever</td>
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<tr>
<td></td>
<td>Splenomegaly</td>
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<td></td>
<td>Cytopenias (affecting ≥ 2 lineages in the peripheral blood):</td>
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<td></td>
<td>- Hemoglobin &lt; 90 g/l (in infants &lt; 4 weeks: hemoglobin &lt; 100 g/l)</td>
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<td></td>
<td>- Platelets &lt; 100,000/ml</td>
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<td></td>
<td>- Neutrophils &lt; 1000/ml</td>
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<td></td>
<td>Hypertriglyceridemia and/or hypofibrinogenemia:</td>
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<td></td>
<td>- Fasting triglycerides ≥ 265 mg/dl</td>
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<td></td>
<td>- Fibrinogen ≤ 1.5 g/L</td>
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<td></td>
<td>Hemophagocytosis in bone marrow or spleen or lymphnodes</td>
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<td></td>
<td>Low or absent NK-cell activity</td>
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<tr>
<td></td>
<td>Ferritin ≥ 500 µg/l</td>
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<td></td>
<td>Soluble CD25 ≥ 2400 U/L</td>
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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 ↓.
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 the rheumatic diseases and are listed in Table II together with a brief comment. HLH was described in systemic lupus erythematosus (SLE) (94 patients), Still's disease (37 patients), rheumatoid arthritis (RA) (13 patients), systemic juvenile arthritis (S-JRA) (219 patients), dermatomyositis (7 patients), Kawasaki disease (25 patients), systemic sclerosis (SSc) (5 pa-

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

<table>
<thead>
<tr>
<th>Systemic disease</th>
<th>References and note</th>
<th>N° parer/cases</th>
</tr>
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<tbody>
<tr>
<td>SLE</td>
<td>14 Retrospective study, 15 cases; 20 Retrospective study, 15 patients; 21 retrospective study, 14 cases; 22 retrospective study, 19 children; 23 retrospective, 2 children; 23 3 cases; 24 18-year-old female, lupus mesenteric vasculitis, EBV reactivation; 33 36-year-old woman; 34 antiphospholipid antibodies; 35 21-year-old man, HLH and SLE simultaneously; 36 38-year-old female, interstitial pneumonia, CMV. Gancyclovir resolved the pancytopenia, pneumonia, and fever; 41 non-Hodgkin's lymphoma; 42,43 35-year-old woman, Graves' disease, parvovirus B19; 45 28-year-old woman; 46 38-year-old woman; 47 41-year-old woman, corticosteroid and cyclophosphamide, lupus nephritis, CMV colitis; 48 CMV-induced hemophagocytic syndrome and colitis; 50 Successful use of etanercept; 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</td>
<td>32 94</td>
</tr>
<tr>
<td>Still's disease</td>
<td>58 Adult patient, interstitial pneumonia with pneumomediastinum/recurrent pneumothorax; 59 40-year-old woman; 60 8-year-old child, acute respiratory failure, coagulopathy; 61 after initiation of sulfasalazine; 62 cases; 63 46-year-old woman, high-dose steroid treatment; 64 CMV; 65 50-year-old female, steroids and antimarial drugs; 66 six patients, one death due to pneumonia, one etanercept; 75 retrospective study 4 cases; 76 retrospective study 4 cases; 77 after initiation of etanercept; 78 16-year-old female successful use of etanercept; 79 18 patients, successful use of infliximab in 2 cases; 80 adult, liver transplant recipient; 81 after initiation of adalimumab, histoplasmosis.</td>
<td>18 37</td>
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<tr>
<td>RA</td>
<td>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; 82,83 76-year-old Japanese woman successfully treated with etanercept</td>
<td>112 13</td>
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<tr>
<td>S-JRA</td>
<td>84 Hypocomplementemia 3 cases; 85 retrospective study. 102 children 854; patients; 86,87,89 misdiagnosed as Kawasaki disease; 88 12 year-old female child, fatal; 90 child after etanercept; 90,92 38 children; 91,93 children; 94 children, etanercept potentially useful for obtaining remission in children not responding to steroids and cyclosporin A; 96 13-month-old boy; 97 five children; 98 14 children; 99 occult MAS in patients who undergo BMA; 100 7 cases in retrospective study; 101 retrospective, 18 children; 102 hepatitis A- report of 2 cases; 103 after initiation of etanercept; 104 successfully treated with etanercept; 105,106 successfully treated with anakinra.</td>
<td>23 219</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>107 Central nervous system lesions and review eight literature cases of dermatomyositis and HLH; 108 17-year-old woman, fatal dermatomyositis with anti-Mi2 antibodies; 109,110 7 years old boy, plasmapheresis; 111 platelet-specific hemophagocytosis; 112 60 year old male.</td>
<td>7 7</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>113,114 3-year-old girl with incomplete Kawasaki disease; 115 16-year-old boy; 116 18-month-old child, respiratory failure, fatal; 117,118 2 cases; 119,120 autoimmune hemolytic anemia; 121,122 32-month-old Japanese boy; 123 2 cases; 124,125 14-year-old boy; 126,127 5-year-old girl, response to gamma-globulin therapy, ischemic colitis; 128 infant of 7 weeks after clinical response to treatment, suddenly died from a myocardial infarction at 11 weeks.</td>
<td>17 25</td>
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</table>
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Active infection was clearly reported in 16 cases of HLH: (4 CMV40,49,50,64, 4 EBV27,28,32,47, one HSV-129, one parvovirus B194, two hepatitis A4, one miliary tuberculosis, steroid, fatal; 132,134, one 23-year-old woman, etoposide; 12632-year-old woman; 124MPO-ANCA positive vasculitis; 24retrospective study 1 case; 12333-year-old woman, etoposide; 12652-year-old woman; 12743-year-old man, EBV; 21retrospective study 2 cases; 31retrospective, 2 children127.

Among SLE patients, HLH occurred in 2 cases after parturition, in 1 case after abortion and in 1 pregnant patient causing preeclampsia and cerebral hemorrhage55-57.

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 cases30.

HLH should be recognized as a severe, potentially life-threatening complication of rheumatic diseases. Since HLH has a mortality rate of 8% to 22%43, 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). 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. 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. SLE is an immunologically mediated disease; therefore either an immune complex-mediated or an autoimmune-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.

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 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.

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 (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 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.

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 plasmapheresis. 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 diseases. A triggering infective cause should be always accurately searched and antinfecive treatment started in the case of active infection.

References


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