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Autoimmune-Associated Hemophagocytic Syndrome/Macrophage Activation Syndrome

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1. Introduction

Hemophagocytic syndrome (HPS), also known as hemophagocytic lymphohistiocytosis (HLH) encompasses an infrequent group of non-malignant, yet potentially life-threatening disorders caused by massive cytokine release from activated lymphocytes and macrophages (Filipovich, 2009; Henter et al., 1998, 2007; Janka et al., 1998; Janka, 2009). This multisystem inflammatory syndrome is associated with a range of genetic and acquired factors. Hectic and persistent fever, cytopenias, hepatitis, jaundice, edema, splenomegaly, neurological symptoms and hemophagocytosis in bone marrow (BM), liver or lymph nodes are common clinicopathological features of HLH.

2. Historical background and terminology of HLH

The first published report on HLH is presumably an observation of hemophagocytosis in malignancy (Tschistowitsch & Bykova, 1928). In 1939, Scott and Robb-Smith reported four similar cases of adults with an HLH-like picture and proposed to call this condition histiocytic medullary reticulosis (HMR) (Scott & Robb-Smith, 1939). The term HMR was later succeeded by the disease entity known as malignant histiocytosis (MH) (Rappaport, 1966). The familial form of HLH (named FHL or FHLH) was first described in a family with two affected siblings (Farquhar & Claireaux, 1952). Risdall et al. later reported a series of 19 patients with active viral infection, whose bone marrow smears disclosed histiocytic hyperplasia with prominent hemophagocytosis (Risdall et al., 1979). Of note, 14 of 19 patients in this study were immunosuppressed and active infection with herpes group viruses was documented in 74% (14/19) of patients. They proposed to term this condition virus-associated hemophagocytic syndrome (VAHS). Some authors argue that this paper by Risdall and colleagues is the first well documented report of acquired (or secondary) HLH (sHLH) (Kumakura, 2005). Five years later, Risdall et al. also reported HPS in three patients with bacterial sepsis (Risdall et al., 1984). This condition was named bacteria-associated

hemophagocytic syndrome (BAHS). To date, sHLH is known to be associated not only with viral or bacterial infections, but also with different types of other disseminated infections, including fungal or parasitic infections (Janka et al., 1998). Therefore, HLH associated with any infection type is collectively called infection-associated hemophagocytic syndrome (IAHS) or infection-associated hemophagocytic lymphohistiocytosis (I-HLH) (Kumakura et al., 2004).

The origin of the proliferating cells in MH has been thought to be the precursors of histiocytes, but then it has been clarified that the proliferating cells are lymphoma cells (Kumakura, 2005). In 1981, a case of T-cell lymphoma resembling MH was reported (Kadin, 1981). Following this report, many lymphoma cases associated with HPS have been reported worldwide (Han et al., 2007; Hasselblom et al., 2004; Ishii et al., 2007; Janka et al., 1998; Reiner & Spivak, 1988; Tong et al., 2008). In most of these cases it was proven that the proliferating cells were not of histiocytic origin, but that they were lymphoma cells. Therefore, the 'true MH', which is recognized as a neoplastic disease of immature histiocytes, is thought to be very infrequent, and secondary HLH associated with lymphoma is called lymphoma-associated hemophagocytic syndrome (LAHS) (Kumakura, 2004). Later, it has become clear that other hematological malignancies (e.g. myelodysplastic syndromes, acute and chronic leukemias, multiple myeloma) and solid cancers (e.g. thymoma, carcinoma, germ cell tumor, hepatocellular carcinoma) can be associated with HLH as well (Gupta et al., 2009; Ishii et al., 2007; Janka et al., 1998; Lackner et al., 2008; Machaczka et al., 2010; Reiner & Spivak, 1988; Shabbir et al., 2010). Thus, HLH associated with any malignancy should be collectively called malignancy-associated hemophagocytic syndrome (MAHS) or malignancy-associated hemophagocytic lymphohistiocytosis (M-HLH).

In 1991, Wong reported six patients with active systemic lupus erythematosus (SLE) who demonstrated reactive bone marrow hemophagocytosis (Wong et al., 1991). Since there was no evidence of an underlying infection, hemophagocytosis was thought to be solely associated with the activity of SLE, and the authors proposed to name this condition acute lupus hemophagocytic syndrome (ALHS). Shortly thereafter, Kumakura et al. reported cases of secondary HLH associated with autoimmune diseases other than SLE, and postulated to consider a new disease entity autoimmune-associated hemophagocytic syndrome (AAHS) (Kumakura et al., 1995, 1997). Albert et al. were the first to use the term 'macrophage activation syndrome' (MAS) in a description of the disorder (Albert et al., 1992). Shortly after, Stephan et al. used the term MAS in their description of 4 children suffering from chronic rheumatic disease characterized by a pro-inflammatory milieu (Stephan et al., 1993). MAS has been often reported in cases of systemic juvenile idiopathic arthritis (sJIA), but is also a known complication of adult onset Still's disease (AOSD), systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjögren's syndrome, dermatomyositis, Kawasaki disease, mixed connective tissue disease and systemic sclerosis (Carvalheiras et al., 2010; Davi et al., 2011; Fukaya et al., 2008; Grom & Mellins, 2010; Hendricks et al., 2010; Kumakura et al., 2004; Parodi et al., 2009; Sawhney et al., 2001; Simonini et al., 2010; Titze et al., 2009; Tristano, 2008).

Recognition in recent years that MAS belongs to the class of sHLH has led to a proposal to rename it according to the contemporary classification of histiocytic disorders (Ramanan & Baildam, 2002). Some authors have suggested that the term MAS be dropped in favor of reactive HLH to reflect this similarity and to better familiarize pediatric rheumatologists with treatment options, particularly in patients not responding to frontline therapy (Grom 2003). Nevertheless, use of the term MAS still remains prevalent in the rheumatology

literature, whereas syndromes described in the hematology and infectious disease literature often describe a similar phenomenon as secondary HLH (Deane et al., 2010). Some authors suggest that the terms MAS and HLH are interchangeable (Behrens, 2008; Behrens et al., 2008; Emmenegger et al., 2005; Ramanan & Baildam, 2002), whereas others describe MAS as a distinct subset of sHLH (Arceci, 2008; Janka, 2007, 2009), and still others highlight the heterogeneity of disorders described by both terms and call for revised terminology based more precisely on pathophysiology (Grom et al., 2003; Grom & Mellins, 2010).

3. Classification of HLH

According to the aforementioned historical background and current progress in understanding of its pathophysiology, HLH is generally divided into two distinct forms: an inherited, familial form and an acquired, secondary form (Arceci 2008; Janka, 2009; Henter et al., 2007). FHL has an autosomal recessive inheritance pattern, and usually arises in infants (80% cases), however in rare cases it can also occur in adults (Gupta & Weitzman, 2010; Henter et al., 1991b, 1998, 2007; Nagafuji et al., 2007). Acquired HLH can develop at any age, from childhood to the elderly, as a result of intensive immunological activation due to severe infections, autoimmune inflammatory disorders or malignancies (Janka, 2009; Henter et al., 2007). HLH as a serious complication of autoimmune diseases is commonly called macrophage activation syndrome or autoimmune-associated hemophagocytic syndrome. Macrophage activation syndrome as a severe complication of the systemic form of juvenile idiopathic arthritis (sJIA) is a prototype of AAHS. Nowadays MAS is considered a special form of acquired HLH by most rheumatologists. However, it should be emphasized that in the literature dealing with HLH in adults, MAS is sometimes used synonymously with acquired HLH regardless of its cause (Janka, 2009). The contemporary classification of HLH is presented in Table 1.

4. Epidemiology of HLH

Until recently, it was widely believed that FHL because of genetic causes arose during infancy and early childhood. In a retrospective Swedish study the incidence of FHL was estimated to be 0.12/100,000 children per year (Henter et al., 1991b). With the more widespread availability of genetic testing, it is apparent that the first significant episode of HLH can occur throughout life from prenatal presentations through to the seventh decade.

There is no exact data on the incidence of any form of the acquired HLH. In 2007, a retrospective study was published analyzing HLH cases diagnosed in Japan between 2001 and 2005 (Ishii et al., 2007). The most frequent form of HLH in all age groups in Japan was EBV-associated HLH (35%; 163/469 pts), followed by other infection–associated HLH (29%; 138/469 pts), lymphoma–associated HLH (18%; 84/469 pts), autoimmune–associated HLH (11%; 53/496), FHL (4.5%; 20/469 pts) and post-HSCT (hematopoietic stem cell transplantation) HLH (2.5%; 11/469 pts). The authors estimated that the annual incidence of all types of HLH and in all age groups of Japanese patients was 1 case in 800,000 individuals per year (Ishii et al., 2007). However, this number is probably underestimated, due to the retrospective nature of the study, certain diagnostic difficulties and overlooking or misdiagnosing of some HLH cases. In the same study, the reported 5-year overall survival was highest in EBV- or other infection-associated HLH (> 80%) and in autoimmune-associated HLH (almost 90%), intermediate in FHL or B-cell lymphoma-associated HLH

(50%), and lowest in T/NK-cell lymphoma-associated HLH (< 15%) (Ishii et al., 2007). A recent retrospective population-based study revealed the annual incidence of M-HLH in adults to be 1:280,000 per year or 0.36/100,000 individuals per year (Machaczka et al., 2011a). The results of this study were limited by the small population of the Swedish region of northern Halland, but the long observation period of over 14 years strengthened these findings.

Genetic HLH			**Acquired HLH**		
Familial HLH	Known gene defects: *?(FHL1)* *PFR1(FHL2)* *UNC13D (FHL3)* *STX11 (FHL4)* *STXBP2 (FHL5)*	Mutation's location: 9q21.3–22 10q21–22 17q25 6q24 19p13	**Infection-associated**	Virus-associated	EBV, CMV, HSV, adenovirus, influenza
				Bacteria-associated	different species
				Fungus-associated	Aspergillus spp., Candida spp., etc.
				Other organisms	Pneumocystis jiroveci, Malaria, Leishmania
	Unknown gene defects	ND	**Autoimmune-associated**	sJIA, adult onset Still's disease, Kawasaki disease, rheumatoid arthritis, vasculitis, polymyositis/dermatomyositis, systemic sclerosis, systemic lupus erythematosus	
Immune deficiency syndromes	Chédiak-Higashi syndrome (*LYST*)	1q42.1–q42.2	**Malignancy-associated**	Lymphoma-associated	T/NK-cell leukemia and lymphoma, B-cell lymphoma, Hodgkin lymphoma
				Other malignancies	Hematological: MDS, AML, ALL, MM Solid tumors: melanoma, thymoma, hepatocellular carcinoma, germ cell tumor
	Griscelli syndrome 2 (*RAB27A*)	15q21	**Immune supression/post-transplantation** immune suppressive therapy post-autologous SCT HLH and post-allogeneic SCT HLH		
	X-linked lymphoproli-pherative syndrome: (*SH2D1A*) (*XIAP*)	 xq25 xq25	**Drug-associated** Anticonvulsants (e.g., phenytoin, carbamazepine)		

HLH – hemophagocytic lymphohistiocytosis; EBV – Epstein-Barr virus; CMV – cytomegalovirus; HSV – herpes simplex virus; ND – not determined; sJIA – systemic onset juvenile idiopathic arthritis; NHL – non-Hodgkin lymphoma; MDS – myelodysplastic syndromes; AML – acute myeloid leukemia; ALL – acute lymphoblastic leukemia; MM – multiple myeloma; SCT – stem cell transplantation.

Table 1. The contemporary classification of different HLH forms

The reported incidence of juvenile idiopathic arthritis (JIA) varies from 1 to 22 cases per 100,000 children, with a prevalence of 8 to 150 cases per 100,000 children (Cassidy & Petty, 2005; Weiss & Ilowite, 2007). Of these, approximately 10% of patients have the systemic form of the disease (i.e., sJIA). It is estimated that approximately 7–10% of patients with sJIA develop life-threatening MAS (Janka, 2009; Sawhney et al., 2001), which may occur at any time during the course of the disease, with a mortality between 10–20%. Moreover, two studies suggested that a mild, subclinical form of MAS may be present in as many as 25–30% patients with sJIA (Bleesing et al., 2007, Behrens et al., 2007). Although there are also numerous reports of MAS in adult onset Still's disease, SLE, and Kawasaki disease, the incidence of MAS in these entities is unknown. However, in considering MAS in general, the mortality rate is presumably about 8–22% (Gupta & Weitzman, 2010).

5. Clinical and laboratory features of HLH and AAHS/MAS

The most typical signs of HLH are fever (duration ≥7 days, with peaks ≥38.5^{o}C) and splenomegaly associated with pancytopenia (affecting ≥2 cell lineages in peripheral blood), cerebromeningeal symptoms, skin rash, lymph node enlargement, jaundice and edema (Henter et al., 1991b; Kumakura, 2005; Öst et al., 1998; Reiner & Spivak, 1988). Laboratory findings include hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, coagulopathy, liver function abnormalities (i.e., elevated transaminases and bilirubin), hypoproteinemia, and hyponatremia (Henter et al., 1991b, 1998, 2007; Janka et al., 1998). Histopathological examination reveals accumulation of lymphocytes and histiocytes (macrophages), sometimes with hemophagocytic activity, observed in the spleen, bone marrow, liver, lymph nodes and cerebrospinal fluid (Henter & Nennesmo, 1997; Henter et al., 2007; Janka, 2009; Öst et al., 1998). The histological picture of liver biopsy resembles chronic persistent hepatitis (Henter et al., 2007). In the brain the leptomeninges and perivascular spaces are involved (Akima & Sumi, 1984; Henter & Nennesmo, 1997). Other typical findings in HLH are low natural killer (NK) cell activity and high levels of the alpha chain of the soluble interleukin-2 receptor (sIL-2R, also named sCD25) in serum and CSF (Henter et al., 2007; Janka, 2009). Soluble IL-2R (together with an elevated level of ferritin) is a marker of generalized inflammation, but very high levels of sIL-2R are almost never seen outside of HLH (Filipovich, 2009). Normal ranges of sIL-2R vary with age being highest in infants, and lower in teenagers and adults. All the key clinical and laboratory features of HLH can be explained by hypercytokinemia and organ infiltration as shown in Table 2 (Janka, 2009).

Another important marker of HLH is soluble CD163 (sCD163). The macrophage hemoglobin scavenger receptor CD163 is restricted in its expression exclusively to cells of the monocyte–macrophage lineage (Schaer et al., 2005). The extracellular part of the protein is shed into plasma (sCD163), because of proteolytic cleavage upon macrophage activation. Thus, sCD163 is a reliable clinical marker of disorders associated with overwhelming macrophage activity (Filipovich, 2009; Grom & Mellins, 2010; Schaer et al., 2005). Because sIL-2R and sCD163 are soluble molecules shed from the surfaces of activated T cells and macrophages, respectively, their levels are likely to increase in the serum regardless of the tissue localization of these cells (Grom & Mellins, 2010).

AAHS/MAS may exhibit all of the characteristic features of HLH. Coagulopathy and cardiac impairment are common (Janka, 2009). Neurological symptoms in MAS may progress to a severe encephalopathy and coma. Of note, not all patients with

HLH symptom/sign	Causative factors
Fever	IL-1; IL-6, TNF-α
Cytopenia in peripheral blood	suppressive acitivity of TNF-α, INF-γ, and the heavy unit of ferritin on hematopoiesis; hemophagocytosis
High concentration of triglycerides in blood	supressive action of increased levels of TNF-α on lipoprotein lipase
Low concentration of fibrinogen in blood	high levels of plasminogen activator secreted by macrophages stimulate plasmine and in consequence lead to hiperfibrynolisis
High concentration of ferritin in serum	released by activated histiocytes/macrophages
High concentration of the α chain of the sIL-2R in blood	secreted by activated T lymphocytes
Hepatosplenomegaly	organ infiltrations with activated lymphocytes and histiocytes/macrophages
Increased liver transaminases and bilirubin in blood	
Neurological abnormalities	

HLH – hemophagocytic lymphohistiocytosis; IL – interleukin; TNF – tumor necrosis factor; sIL-2R – soluble IL-2 receptor (also named sCD25).

Table 2. Signs and symptoms of HLH and their causes

autoimmune/autoinflamatory diseases and MAS fulfill at the beginning diagnostic criteria for HLH (Janka, 2009). In patients, who already have signs of inflammation such as high leukocytosis, elevated platelet count, and elevated levels of fibrinogen, a decline in these parameters, without reaching pathological values, may herald MAS (Ravelli et al., 2005). MAS as a first symptom of sJIA may be indistinguishable from other cases of HLH when arthritis is missing. A high interleukin-1β concentration in blood may also suggest MAS rather than classic HLH (Janka, 2009; Henter et al., 1996). Although mild elevation of sIL-2R has been reported in many rheumatic diseases including JIA and SLE, a several-fold increase in the levels of sIL-2R in these diseases is highly suggestive of MAS (Grom & Mellins, 2010). Importantly, other clinical entities associated with high levels of sIL-2R include malignancies and some viral infections, such as viral hepatitis, and so these conditions should be considered in the differential diagnosis. Nevertheless, sIL-2R receptor and sCD163 are now increasingly recognized as important biomarkers of AAHS/MAS (Filipovich, 2009; Grom & Mellins, 2010).

6. Diagnosis of HLH and AAHS/MAS

In 1991 the HLH Study Group of the Histiocyte Society published the first diagnostic guidelines for HLH which were later updated in 2004 (Henter et al., 1991c, 2007). According to the current guidelines (HLH-2004), five of the following eight criteria must be fulfilled for the diagnosis of HLH: (1) fever, (2) splenomegaly, (3) cytopenias affecting two or three

lineages (Hb <90 g/l; PLT <100 × 10^9/l; neutrophils <1.0 × 10^9/l), (4) hypertriglyceridemia (fasting triglycerides >3.0 mmol/l) and/or hypofibrinogenemia (<1.5 g/l), (5) hemophagocytosis in bone marrow, spleen, or lymph nodes, (6) hyperferritinemia (>500 μg/l), (7) low or absent NK-cell activity, (8) elevated level of sIL-2R (sCD25) >2400 U/ml. The last three HLH criteria were introduced in the revised diagnostic guidelines for HLH in 2004 (Henter et al., 2007).

There are no validated diagnostic criteria addressed exclusively for AAHS/MAS, and early diagnosis is often difficult (Filipovich et al., 2010; Fukaya et al., 2008; Grom & Mellins, 2010). In general, in a patient with persistently active underlying rheumatologic disease, a fall in the ESR and platelet count, particularly in combination with persistently high CRP and increasing levels of serum D-dimer and ferritin, should raise a suspicion of impeding MAS (Grom & Mellins, 2010). According to Janka, a C-reactive protein >100 mg/l, increased granulopoiesis with left shift in the bone marrow and peripheral blood, and s-ferritin concentration >10,000 μg/L (if EBV infection has been excluded) are features strongly suggestive of MAS (Janka, 2009). The diagnosis of MAS is usually confirmed by demonstration of hemophagocytosis in the bone marrow, liver, lymph nodes, etc. However, false negative results may occur owing to sampling errors, particularly at the early stages of the syndrome (Grom & Mellins, 2010; Janka 2009). In some patients, subsequent biopsies may reveal hemophagocytic macrophages. In patients with negative bone marrow biopsies, assessment of the levels of sIL-2R and sCD163 in serum may help with the timely diagnosis of MAS (Grom & Mellins, 2010; Komp et al., 1989; Schaer et al., 2005).

In particular, application of the HLH diagnostic criteria to sJIA patients with suspected MAS is problematic. Some of the HLH markers such as lymphadenopathy, splenomegaly, and hyperferritinemia are common features of active sJIA itself and therefore do not distinguish MAS from a conventional systemic JIA flare (Davi et al., 2011; Grom & Mellins, 2010). Other HLH criteria, such as cytopenias and hypofibrinogenemia, become evident only at the late stages. This is related to the fact that sJIA patients often have increased white blood cell and platelet counts and elevated s-fibrinogen as a part of the inflammatory response in sJIA. Therefore, when they develop MAS, they demonstrate cytopenias and hypofibrinogenemia to the extent seen in HLH only at the later stage of MAS, when its management becomes challenging (Davi et al., 2011; Grom & Mellins, 2010). Diagnosis of MAS is even more problematic in SLE patients with autoimmune cytopenias, which are difficult to distinguish from cytopenias caused by MAS (Carvalheiras et al., 2010; Grom & Mellins, 2010; Parodi et al., 2009). In these patients, the presence of extreme hyperferritinemia and elevated LDH should raise suspicion of MAS (Parodi et al., 2009). Attempts to modify the HLH criteria to increase their sensitivity and specificity for the diagnosis of MAS in rheumatic conditions have been initiated and continue today (Ravelli et al., 2005; Davi et al., 2011).

7. Case presentations

Here we present three illustrative cases of patients with different autoimmune diseases developing severe AAHS/MAS in the course of their autoimmune disorder.

7.1 MAS complicating juvenile arthritis and ankylosing spondylitis

A 31-year-old male was referred from community hospital to the University Hospital (The Second Chair of Internal Medicine, Collegium Medicum, Jagiellonian University, Krakow,

Poland) because of persistent fever and progressive haemostatic abnormalities (skin bruises, undetectable fibrinogen level, prolonged aPTT and INR, markedly elevated FDP and D-dimer levels). The patient was admitted to a community hospital 3 weeks earlier with signs of a possible upper respiratory tract infection (fever, dry cough, sore throat) accompanied by herpes labialis. Broad spectrum antibiotic and acyclovir treatment were both ineffective. Because of a progressing bi-cytopenia (thrombocytopenia with neutropenia; Fig. 1) a fine needle bone marrow biopsy was performed showing no signs of significant primary bone marrow suppression.

Past medical history revealed that the patient suffered from a polyarticular seropositive juvenile arthritis since the age of 8 years. In the following years the patient was hospitalized several times because of disease exacerbations. Non-steroidal inflammatory drugs, gold salts, azathioprine, methotrexate and systemic corticosteroids together with physiotherapy were administered at various time periods; synoviectomy was performed twice. At the age of 29 a diagnosis of ankylosing spondylitis was established (sacroilitis, presence of HLA-B27). Approximately 5 months before admission to our Center the patient's immunosuppressive treatment was modified because of poor disease control, and he received a TNF-α inhibitor (adalimumab) with good clinical response.

On admission the patient complained of pain localized to the right subcostal region and persistent fever. On physical examination body temperature was 39.2°C, and slight hepatomegaly and skin ecchymoses with mucosal bleeding were present. Selected laboratory results and hematologic parameters at admission are shown in Table 3.

Differential diagnosis included DIC with sepsis (blood cultures later showed negative results), neutropenic fever (neutrophils 0.29 × 10^9/l), and opportunistic infections (HBV, HCV, EBV, CMV, and HIV infection were excluded). Adalimumab side effects were also taken into consideration. Filgrastim, ganciclovir and intravenous gammaglobulins were instituted with no improvement. Concomitant medications included ceftazidime, vancomycin, amikacin, sulfamethoxazole/trimethoprim, linezolide, tranexamic acid, fresh frozen plasma and cryoprecipitate.

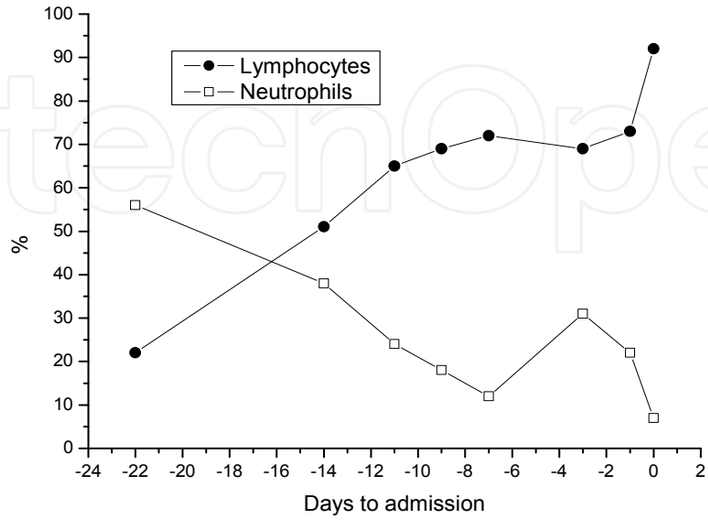


Fig. 1. Changes in neutrophils and lymphocyte counts before the admission

Hematological parameters		Reference range	Patient's result
Hemoglobin	g/l	120–170	99
White blood cells	× 10^9/l	4.0–10	1.0
Lymphocytes	%	20–40	64
Neutrophils	%	58–66	29
Platelets	× 10^9/l	150–400	90
Reticulocytes	‰	3–15	2
Biochemistry			
AspAT	U/l	17–59	263
AlAT	U/l	21–72	116
LDH	U/l	313–618	7,700
CRP	mg/l	<5	56.1
Coagulation tests			
INR		0.85–1.15	1.30
aPTT	sec	25–31.5	55.60
Fibrinogen	g/l	1.8–3.5	undetectable
Fibrinogen (nephelometry)	g/l	1.8–3.5	0.7
Trombin time	sec	14–21	60.1
D-dimer	ng/ml	<500	>10,000
Factor II	%	70–120	45.9
Factor V	%	70–120	106.5
Factor VII	%	70–120	109.7
Factor VIII	%	50–120	39.8
Factor IX	%	70–120	94.6
Factor X	%	70–120	76.2
Factor XI	%	70–120	110.9
Factor XII	%	70–120	81.5

Table 3. The patient's laboratory results on admission

Because of a rapidly progressive thrombocytopenia and neutropenia, bone marrow biopsy was reinterpreted towards a diagnosis of hemophagocytic syndrome. Multiple macrophages (10–15% of nucleated bone marrow cells) together with several hemophagocytes were found (Fig. 2).

A diagnosis of macrophage activation syndrome complicating recent adalimumab treatment was established. Six days after the patient's admission, treatment with etoposide, dexamethasone, and cyclosporine A was instituted as recommended by the modified HLH-2004 protocol (Fig. 3). Body temperature normalized at day 3 of therapy. Etoposide-related

nadir occurred at day 20 (platelets 14 × 10^9/l; leukocytes 0.42 × 10^9/l) (Table 4). One dose of etoposide was omitted and filgrastim (G-CSF) was administered (48 mln units b.i.d) with a beneficial effect. Etoposide was then continued for the next 9 months.

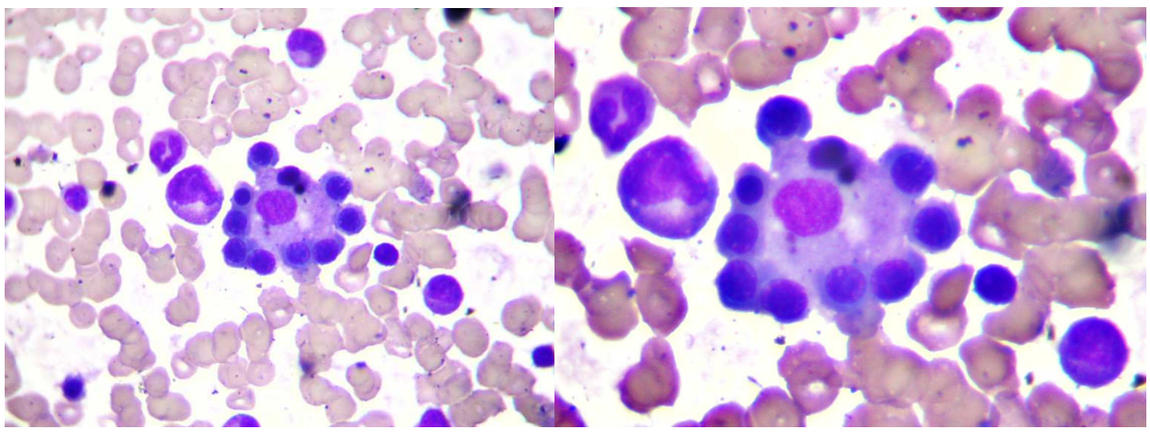


Fig. 2. Bone marrow aspirate smears showing the centrally placed macrophage laden with erythroblasts. Normally developed myeloid cells are present nearby. Wright's stain, lower (× 400) and higher (× 1000) magnification

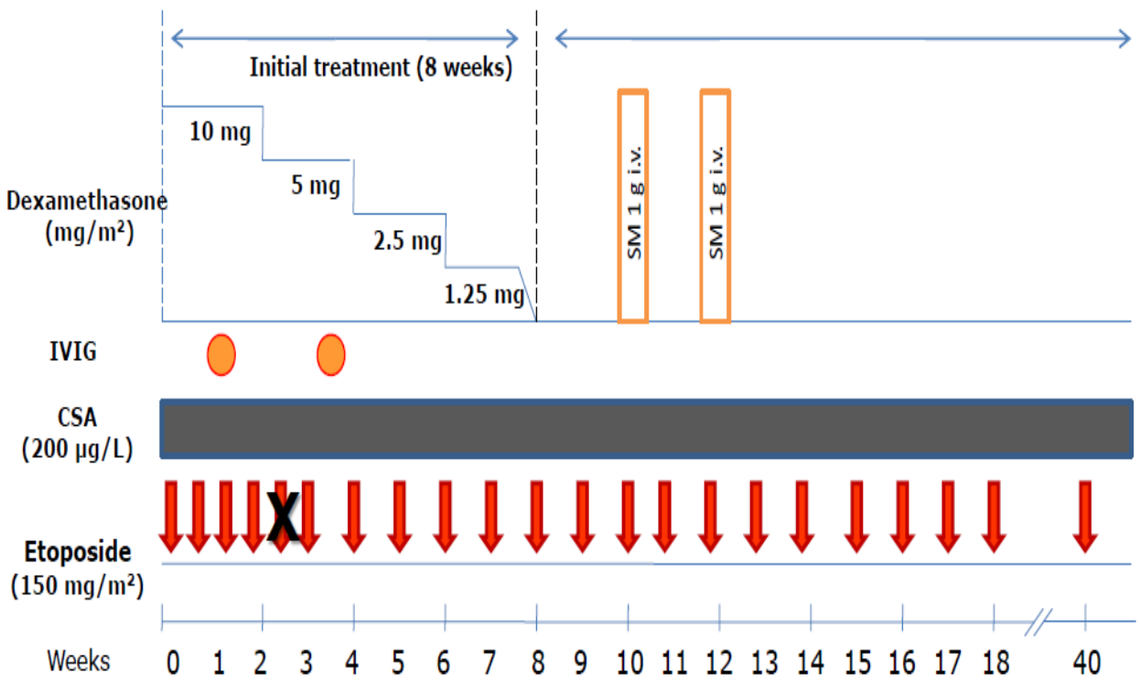


Fig. 3. The patient's treatment scheme with a HLH-2004 protocol

Control examination of bone marrow with a fine needle biopsy performed at week 40 of treatment confirmed the disappearance of activated macrophages. The patient felt well and continues treatment with cyclosporine and low-dose corticosteroids.

Parameter (units)	Baseline (nadir/zenith)	After treatment
Fever (°C)	39.2	35.8
Splenomegaly	slight	-
Hepatomegaly	+	-
Hemoglobin (g/l)	85	137
Platelets (× 10^9/l)	14	260
Neutrophils (× 10^9/l)	0.29	5.3
Triglycerides (mmol/l)	6.5	2.84
Fibrinogen (g/l)	undetectable	4.8
Ferritin (µg/l)	>20,000	233.2
AlAT (U/l)	116	25
Bilirubin (µmol/l)	19	15
LDH (U/l)	7,687	624
Hemophagocytosis	+	-

Table 4. Changes in selected laboratory and clinical parameters characteristic for MAS during the applied therapy (HLH-2004)

7.2 MAS complicating rheumatoid arthritis

A 58-years-old patient, suffering from rheumatoid arthritis for 12 years, about 13 months after a course of TNF-α inhibitor (etanercept) treatment was admitted to hospital in another country due to progressive weakness, weight loss, intensive ankle joint pain and fever reaching 40°C. RA flare and infection were excluded and etanercept-related bone marrow dysfunction was suspected due to agranulocytosis, leukopenia, and thrombocytopenia. The patient had decided to leave the hospital and sought consultation in our University Hospital (The Second Chair of Internal Medicine, Collegium Medicum of the Jagiellonian University, Krakow, Poland). On admission his general condition was satisfactory; physical examination having revealed *livedo reticularis* on the lower limbs, swelling and redness of the left ankle joint, slight splenomegaly and caries of teeth 11 and 24. The most important laboratory abnormalities are shown in Table 5. Rheumatoid arthritis with Felty syndrome was diagnosed 12 years ago based on the presence of 5 ACR criteria, positive rheumatoid factor (RF) and elevated anti-cyclic citrullinated peptide antibodies (anti-CCP). About a year ago etanercept was started due to the ineffectiveness of corticosteroids and methotrexate.

After admission the patient received three injections of filgrastim (48 mln. units each) and antimicrobial treatment was implemented (ceftazidim, amikacin, fluconazole). Teeth 11 and 24 were extracted. The patient was seen by a hematologist and a fine needle bone marrow biopsy was performed showing numerous, typical hemophagocytes (Figure 4).

A macrophage activation syndrome associated with rheumatic disease (RA) was diagnosed. On day 8 of hospitalization, dexamethasone (20 mg qd) and cyclosporine A (dose adjusted to trough blood levels) were initiated. Treatment led to a quick decrease in body temperature and little later to normalization of the peripheral blood picture (Table 6).

Hematological parameters		Reference range	Patient's result
Hemoglobin	g/l	120–170	108
White blood cells	× 10^9/l	4.0–10	0.62
Lymphocytes	%	20–40	80
Neutrophils	%	58–66	13
Platelets	× 10^9/l	150–400	56
Reticulocytes	‰	3–15	43
Biochemistry			
AspAT	U/l	21–72	16
AlAT	U/l	21–72	11
Bilirubin	μmol/l	3–22	12
LDH	U/l	313–618	420
CRP	mg/l	<5	54.3
Coagulation tests			
INR		0.85–1.15	1.08
aPTT	sec	25–31.5	31
Fibrinogen	g/l	1.8–3.5	1.5

Table 5. The patient's laboratory results on admission to the University Hospital

Parameter (units)	Baseline (nadir/zenith)	After treatment
Fever (°C)	37.2	36.6
Splenomegaly	+	-
Hepatomegaly	-	-
Hemoglobin (g/l)	108	133
Platelets (× 10^9/l)	25.2	173
Neutrophils (× 10^9/l)	0.6	3.43
Triglycerides (mmol/l)	2.83	2.7
Fibrinogen (g/l)	1.40	5.2
Ferritin (μg/l)	1,855	717.5
AlAT (U/l)	16	52
Bilirubin (μmol/l)	12	not determined
LDH (U/l)	420	not determined
Hemophagocytosis	+	not determined

Table 6. Changes of selected laboratory and clinical parameters of MAS during the treatment with modified HLH-2004 protocol

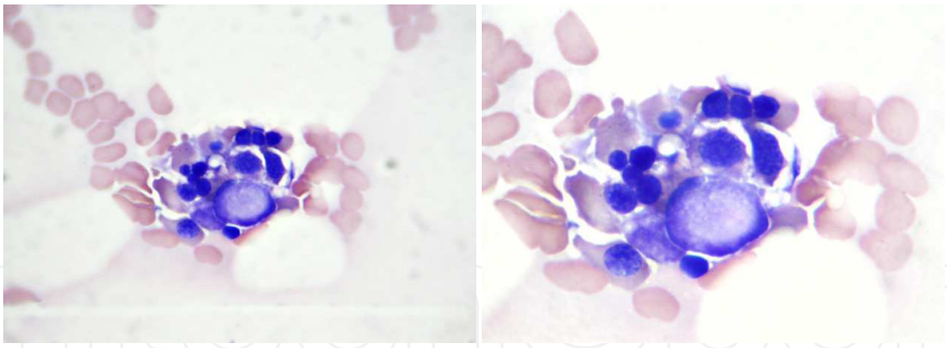


Fig. 4. Bone marrow aspirate smears. The centrally located macrophage shows phagocytosis of erythrocytes, erythroblasts and myeloid cells. Wright's stain, lower (× 400) and higher (× 1000) magnification

7.3 MAS complicating systemic lupus erythematosus

A 46-year-old man was admitted to the University Hospital (The Second Chair of Internal Medicine, Collegium Medicum of the Jagiellonian University, Krakow, Poland) in 2010 because of persistent fever and pulmonary nodules and consolidations. He has been treated for the last 10 years for systemic lupus erythematosus (SLE) with renal involvement. His SLE was diagnosed in 1991 based on the presence of several ARA criteria (fever, arthralgias, pleuritis and pericarditis, proteinuria, anemia, and the presence of ANA in high titer as well as ds-DNA antibodies) and typical results of renal biopsy. His medical history revealed arterial hypertension, peripherial artery occlusive disease and deep vein thrombosis of both lower limbs. Initially SLE was treated with corticosteroids and oral cyclophosphamide, then treatment was frequently modified according to the disease activity (azathioprine, cyclosporine A, mycophenolate mofetil and plasmapheresis).

Hematological parameters		**Reference range**	**Patient's result**
Hemoglobin	g/l	120–150	134
White blood cells	× 10^9/l	4.0–10	9.0
Lymphocytes	%	20–40	12.2
Neutrophils	%	58–66	83.0
Platelets	× 10^9/l	150–400	57
Reticulocytes	‰	3–15	10
Biochemistry			
AspAT	U/l	21–72	38
AlAT	U/L	21–72	50
Bilirubin	μmol/l	3–22	11
LDH	U/l	313–618	1,114
CRP	mg/l	<5	75.7
Coagulation tests			
INR		0.85–1.15	0.94
aPTT	sec	25–31.5	25.9
Fibrinogen	g/l	1.8–3.5	5.0

Table 7. The patient's laboratory results on admission to the University Hospital

The patient's general condition on admission was satisfactory. His body temperature was 38.4°C, physical examination revealed neither hepatosplenomegaly nor lymphadenopathy. Selected laboratory results and hematologic parameters on admission are shown in Table 7. Microbial analysis of bronchoalveolar lavage obtained at bronchoscopy revealed a group I Mycobacteria-other-than-tuberculosis (MOTT). Targeted therapy was instituted (rifampicin 450 mg qd, isoniazide 250 mg qd, ethambutol 750 mg qd and clarithromycin 1000 mg bid) with no effect on the fever. Because of the persistent fever, bronchoscopy was repeated one month later, but MOTT's were no longer detectable. Due to the progressive anemia and thrombocytopenia a fine needle bone marrow biopsy was performed showing typical hemophagocytes, with some of these forming cell conglomerates (Fig. 5).

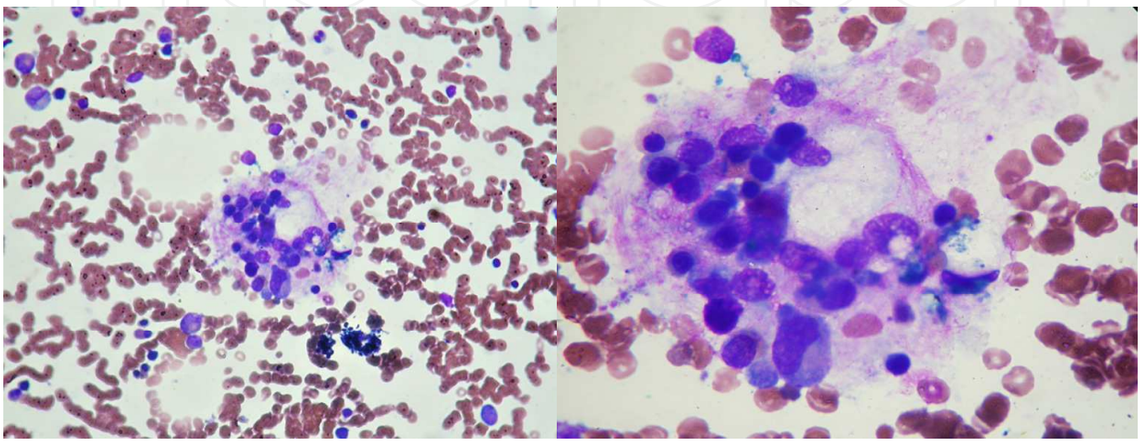


Fig. 5. Wright's stain of bone marrow aspirate smears. The centrally placed large cell conglomerate consists of activated macrophages presenting hemophagocytosis of erythroblasts and myeloid cells. Lower (× 200) and higher (× 400) magnification

Parameter (units)	Reference range	Baseline (nadir/zenith)	After treatment
Fever (°C)		40.0	36.5
Splenomegaly		-	-
Hepatomegaly		-	-
Hemoglobin (g/l)	120–170	85	153
Platelets (× 10^9/l)	150–400	42.2	118.2
Neutrophils (× 10^9/l)		6,100	3,500
Triglycerides (mmol/l)	0.3–2.26	2.63	1.07
Fibrinogen (g/l)	1.8–3.5	3.60	3.1
Ferritin (µg/l)	13–400	1,387	105
AlAT (U/L)	21–72	142	57
Bilirubin (µmol/l)	3–22	12	11
LDH (U/L)	313–618	804	452
Hemophagocytosis		++	single cells

Table 8. Changes of selected laboratory and clinical parameters typical for MAS during treatment (HLH-2004)

Macrophage activation syndrome was diagnosed and one month after the patient's admission treatment with dexamethasone, cyclosporine A, and etoposide was started resulting in the normalization of body temperature and peripherial blood morphology. Etoposide-related nadir occurred at day 14 (platelets 18 × 10^9/l, leukocytes 1.0 × 10^9/l). Two etoposide doses were omitted and filgrastim was administered twice (48 mln units qd). Intravenous pulses of etoposide were given for the next 2 months, followed by oral administration. A control bone marrow examination performed on week 40 of treatment showed disappearance of activated macrophages. The patient has continued treatment with cyclosporine A in combination with low-dose corticosteroids with continuous improvement of his clinical and laboratory parameters (Table 8).

8. Pathophysiologic and molecular mechanism of HLH

Although significant progress in understanding the genetics and pathophysiology of primary HLH has been achieved during recent years, the pathogenesis of acquired forms of HLH is still not fully understood. An exaggerated immune response is the final common pathway of HLH, however, there are multiple roads leading to it (Arceci, 2008; Janka, 2009). The immune response is often triggered by different stimulants (e.g., infection) and the underlying inherited or acquired immune defect. It has been proposed that the clinical presentation of HLH is due to uncontrolled activation of immune cells, macrophages and $CD8^+$ T lymphocytes (cytotoxic), leading to a massive release of various mediators of inflammation such as TNF-α (tumor necrosis factor α), interleukin(IL)-6, IL-8, IL-10, IL-12, IL-18, interferon γ, macrophage inflammatory protein (MIP 1-α), and hematopoietic growth factors (e.g., GM-CSF) (Filipovich, 2009; Henter et al., 1991a, 1996, 2007; Janka & Schneider, 2004; Osugi et al., 1997). IL-10 with its anti-inflammatory properties plays many important roles in the regulation of autoimmune inflammatory responses, particularly of systemic autoimmune disorders such as HLH/MAS. The role of IL-10 as part of an important regulatory mechanism involved in HLH has long been proposed (Behrens et al., 2011; Benveniste et al., 2000; Osugi et al., 1997). Recently, the roles of T regulatory cells in HLH have also been discussed (Verbsky & Grossman, 2006). Low or absent NK-cell function is present in many HLH patients and results in difficulties in termination of the exaggerated immune response (Filipovich, 2009; Henter et al., 2007).

There are two major subtypes of genetic causes of HLH. First are those genetic defects, grouped under the term FHL, that present with HLH as the primary and only manifestation of disease (Gupta & Weitzman, 2010; Henter et al., 2007). A second group of genetic disorders include HLH as only one, although often fatal, manifestation of the disease (Gupta & Weitzman, 2010; Janka, 2009). All known genetic abnormalities causing FHL involve genes that regulate proteins important in the secretory cytolytic pathway of NK-cells and $CD8^+$ T lymphocytes. In 1999, the first FHL-inked locus was discovered on chromosome 9q21.3–22 in several Pakistani families and was later defined as the FHL1 subtype (Ohadi et al., 1999). Shortly thereafter, mutations in the perforin gene *PRF1* were discovered on chromosome 10q21 in a group of patients with FHL (FHL2 subtype) (Stepp et al., 1999). Furthermore, mutations in genes *UNC13D* (located on chromosome 17q25; FHL3 subtype), *STX11* (located on chromosome 6q24; FHL4 subtype), and most recently *STXBP2* (located on chromosome 19p13; FHL5 subtype) were described (Feldmann 2003; zur Stadt et al., 2005, 2009). In view of the remarkable progress since the discovery of the first genetic defect in

FHL in 1999, it is expected that many new mutations in the known genes will be identified, as well as some novel gene mutations (Gupta & Weitzman, 2010).
Viruses, non-steroidal anti-inflammatory drugs, methotrexate, gold salts, and even TNF-α inhibitors have been reported as triggers for AAHS/MAS (Gupta & Weitzman, 2010). Interestingly, distinctions between genetically determined and acquired HLH become increasingly blurred as brand new genetic causes are identified, and patients who develop HLH beyond early childhood or in the contexts of EBV infection or autoimmune disease are being found to share some of the same genetic etiologies (Arceci, 2008; Hazen et al., 2008; Nagafuji et al., 2007; Zhang et al., 2008). Patients who develop sHLH may also have a genetic predisposition, but the molecular basis of the defects in sHLH has yet to be discovered (Arceci, 2008). This supposition has recently been strengthened by recent studies showing decreased NK cell function or reduced perforin expression in children with sJIA complicated by MAS, similarly to patients with FHL (Grom et al., 2003; Wulffraat et al., 2003). Of note, mutations in *UNC13D* gene, mutated in FHL type 3, were also described in patients with sJIA (Hazen et al., 2008; Zhang et al., 2008).

9. Treatment of HLH and AAHS/MAS

Early diagnosis and the prompt introduction of adequate therapy to produce a rapid response are crucial for a positive outcome in HLH. The treatment of any HLH type should focus on: (1) suppression of the hyperinflammatory state by destruction of activated $CD8^+$ T lymphocytes and macrophages, and (2) treatment of any existing triggers (Gupta & Weitzman, 2010; Henter et al., 2007). In cases of FHL, an additional aim is the correction of the underlying immune defect (Filipovich, 2009; Henter et al., 2007; Janka, 2009). HLH treatment categories include: (1) proapoptotic chemotherapy with etoposide (100–150 mg/m²/dose i.v.), and (2) immunosuppressive drugs, targeting the hyperactivated macrophages (e.g., etoposide, corticosteroids, intravenous immunoglobulin), and T lymphocytes (e.g., corticosteroids, cyclosporine A [CyA]) (Henter et al., 2007). In 1994 the first prospective international treatment protocol (HLH-94) was introduced (Henetr et al., 1997). The experience from the HLH-94 protocol (including etoposide and dexamethasone [DXM]) and other studies have led to the development of a new treatment protocol, HLH-2004 (including etoposide, DXM, CyA) (Henter et al., 2007). However, immunochemotherapy (i.e., HLH-94 and HLH-2004 protocols) is only temporarily effective in the control of FHL, and the outcome is uniformly fatal unless the patient undergoes allogeneic stem cell transplantation (alloSCT) (Jordan & Filipovich, 2008; Henter et al., 2007).
Last but not least, since patients with HLH represent a unique population with high morbidity/mortality and disease-specific complications, consideration should be given to referring these patients to centers with significant experience in the treatment and care of HLH.

9.1 Immunochemotherapy

Initially mild cases of HLH can deteriorate rapidly within a short period of time. Therefore, prompt administration of effective HLH therapy may prevent development of the full-blown syndrome. So far, treatment of AAHS/MAS is not standardized and remains highly variable across clinical centers (Deane et al., 2010). Nevertheless, a frontline treatment of AAHS/MAS (particularly of milder grades) usually involves corticosteroids with or without

intravenous immunoglobulin (IVIG), which may be sufficient to control hyperinflammation (Janka, 2009). In order to achieve rapid reversal of the coagulation abnormalities and cytopenias, most clinicians prefer starting with intraveneous methylprednisolone pulse therapy (30 mg/kg for 3 consecutive days) followed by 2 to 3 mg/kg/day divided by 4 doses (Filipovich et al., 2010). After improvement of the complete blood count and resolution of the coagulopathy, steroids are tapered slowly to avoid relapses of MAS (Janka, 2009; Filipovich et al., 2010). High-dose corticosteroids alone have been reported to induce remission in approximately half of MAS patients (Sawhney et al., 2001 Stephan et al., 2001).
Administration of IVIG might be effective in AAHS/MAS. High dose IVIG infusions are immunosuppressive, in part engaging Fc-receptors, which can play an important role in same patients with autoimmune/autoinflammatory diseases (Arceci, 2008; Kumakura et al., 2004). IVIG may also provide an anti-pathogen effect, which is particularly important if MAS is triggered by a viral infection.
Even when treatment is introduced in a timely manner, MAS can be fatal and deaths have been reported among patients treated with massive doses of steroids (Filipovich et al., 2010). However, corticosteroid resistant non-responders may benefit from second-line therapies, such as CyA or etoposide. Parenteral administration of CyA has been shown to be effective in patients with corticosteroid-resistant MAS (Mouy et al., 1996; Ravelli et al., 1996). Of note, in author's experience, some patients with MAS have not responded until etoposide was added to the HLH therapy. The similar conclusion has recently been postulated by other authors (Gupta & Weitzman, 2010). Thus, if there is no response to the aforementioned drugs (corticosteroids, IVIG, CyA), use of the HLH-2004 protocol including etoposide is recommended (Table 9). In summary, patients with suspected AAHS/MAS could be started on therapy without etoposide, as long as treatment adjustments are made rapidly in refractory cases (Gupta & Weitzman, 2010).
The utility of biological response modifiers in MAS treatment remains unclear, and at the present there is no consensus on recommendations in respect to this group of drugs. The use of TNF-α inhibitors (etanercept, infliximab) in MAS has produced conflicting results, being the effective therapy in some patients (Makay et al., 2008; Sellmer et al., 2011), while triggering MAS in others (Sandhu et al., 2007). Biological agents that neutralize IL-1 (anakinra) and IL-6 (tocilizumab) have been reported to be effective in occasional MAS patients (Filipovich et al., 2010; Kelly & Ramanan, 2008), but the clinical experience is as yet limited. In the case of patients with a form of sHLH other than AAHS/MAS, which proved refractory to frontline HLH therapy, anecdotal reports on the beneficial use of plasma exchange, hemofiltration, antithrombin III, anti-CD52 antibodies (alemtuzumab), and anti-CD25 antibodies (daclizumab) have been published previously, but the role of these therapies is not yet validated for any type of HLH (Gupta & Weitzman, 2010). Lastly, if MAS is driven by EBV infection, monoclonal anti-CD20 antibodies (rituximab) which deplete B lymphocytes, the main type of cells harboring EBV virus, should be used (Balamuth et al., 2007).

9.2 Stem cell transplantation

The first successful allogeneic bone marrow transplantation in a case of HLH was reported in 1986 (Fischer et al., 1986). Since then, information regarding the role of alloSCT in the treatment of HLH has mostly concerned FHL (Janka, 2009; Marsh et al., 2010). In FHL, alloSCT is the only available curative treatment option with the reported 5-year overall

	Children	Adults*
Initial therapy (weeks 1–8) aiming remission of HLH	**Etoposide**	
	150 mg/m² i.v. twice weekly in 2 weeks followed by once weekly administration (week 3–8)	50–120 mg/m² i.v. twice weekly in 2 weeks followed by once weekly administration (week 3–8)
	Caution! Adults usually do not tolerate as high etoposide doses as children, therefore dose reduction is indicated as proposed above	
	Dexamethasone	
	10 mg/m² p.o. daily in 2 weeks (week 1–2) 5 mg/m² p.o. daily in 2 weeks (week 3–4) 2.5 mg/m² p.o. daily in 2 weeks (week 5–6) 1.25 mg/m² p.o. daily in 1 week (week 7) tapering and discontinuation during week 8	
	Cyclosporine A	
	3 mg/kg p.o. twice daily during the first week of therapy, followed by dose aiming CyA concentration at trough of 200 μg/l (week 2–8)	
	Caution! Adults usually do not tolerate as high CyA concentrations as children, and CyA concentrations of 100–200 μg/l may be acceptable	
	General remarks:	
	1. Maximal initial supportive care is suggested, inclusive: appropriate broad-spectrum antibiotics (until culture results); prophylactic co-trimoxazole (equivalent to 5 mg/kg of trimethoprim 3 times weekly); an oral antimycotic therapy; antiviral therapy in patients with ongoing viral infection; and IVIG (0.5 g/kg) once every 4 weeks	
	2. Gastroprotection due to the high steroids doses is recommended (e.g., PPIs)	
	3. If after 2 weeks there is clinical evidence of progressive neurological symptoms or if abnormal CSF (pleocytosis and elevated proteins) has not improved, 4 weekly intrathecal Methotrexate injections are recommended	
Continuation therapy (≥ week 9) after achieved HLH remission until alloSCT or therapy discontinuation	**Etoposide**	
	150 mg/m² i.v. once weekly every alternating (with Dexamethasone) second week	50–100 mg/m² i.v. once weekly every alternating (with Dexamethasone) second week
	Dexamethasone	
	pulses of 10 mg/m² p.o. for 3 consecutive days, given every alternating (with etoposide) second week	
	Cyclosporine A	
	dose aiming CyA concentration at trough of 200 μg/l (adults 100–200 μg/l)	

* – etoposide dose recommendations for adults are not validated proposal, but based on clinical experience (personal communication with Jan-Inge Henter)
HLH - hemophagocytic lymphohistiocytosis; CSF – cerebrospinal fluid; CyA – cyclosporine A; IVIG - intravenous immunoglobulin; PPI – proton pump inhibitor.

Table 9. The HLH-2004 immunochemotherapy protocol for management of hemophagocytic lymphohistiocytosis

survival rate of 50–70% with myeloablative conditioning (MAC) (Baker et al., 1997; Cesaro et al., 2008; Dürken et al., 1999; Horne et al., 2005; Imashuku et al., 1999; Jabado et al., 1997; Ouachèe-Chardin et al., 2006), and 75–92% with reduced-intensity conditioning (RIC) (Cooper et al., 2006; Marsh et al., 2010).

So far, alloSCT has been performed only occasionally in cases of acquired HLH and its role in the treatment of sHLH is not yet established. Sporadic case reports have previously been published on refractory EBV-HLH successfully treated by means of alloSCT (Minegishi et al., 2001; Sovinz et al., 2010; Toubo et al., 2004). A recent Japanese survey revealed a curative effect of alloSCT on sHLH in 7 out of 11 patients (64%) with refractory EBV-HLH (Ogha et al., 2010). Similarly, Yoon et al. reported that alloSCT could be a curative treatment not only for FHL, but also for relapsed/refractory sHLH (Yoon et al., 2010). Anecdotal reports have also shown the efficacy of alloSCT in M-HLH therapy (Chang et al., 2009; Goi et al., 1999; Kelly et al., 2011; Machaczka et al., 2011b).

No concerted effort to apply alloSCT for the definitive treatment of MAS has yet been made. Given the high mortality associated with the current management of AAHS/MAS, the option of alloSCT using less intensive conditioning protocols, is reasonable to consider, especially in cases of severe or recurrent MAS episodes (Filipovich et al., 2010). Of note, sometimes fatal MAS was observed as a complication of prolonged T lymphocyte immunodeficiency in early trials of autologous stem cell transplantation for severe progressive systemic or polyarticular juvenile idiopathic arthritis (Filipovich et al., 2010). These observations suggested a failure to control the underlying disease given the patient's genetically predisposed hematopoietic stem cells (Bleesing et al., 2007).

10. Conclusions

Autoimmune-associated hemophagocytic syndrome/macrophage activation syndrome is a life-threatening hyperinflammatory syndrome which remains a major cause of morbidity and mortality in patients with autoimmune/autoinflammatory diseases. Awareness of AAHS/MAS, its symptoms and diagnostic criteria should be made mandatory among all physicians, especially those providing care to patients with autoimmune/autoinflammatory diseases. There are no validated diagnostic criteria making early MAS diagnosis difficult in part owing to strong similarities between MAS and sepsis. The treatment of MAS remains highly variable across clinical centers. Nevertheless, the frontline treatment of AAHS/MAS usually involves corticosteroids with or without intravenous immunoglobulin. In some patients with corticosteroid-refractory MAS, administration of cyclosporine A circumvents refractoriness. If there is no response to the aforementioned treatments a use of etoposide is recommended. The progress in understanding the pathophysiology behind MAS and identification of the pathways associated with the early stages of this syndrome bring hope to the idea of developing new biomarkers and treatments for clinical practice.

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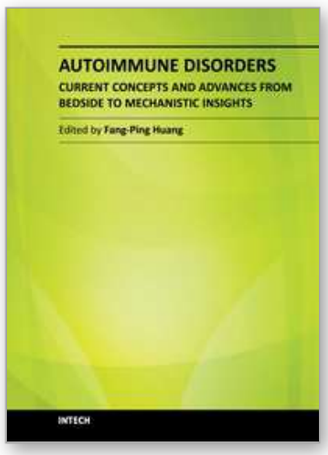
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Autoimmune disorders are caused due to break down of the immune system, which consequently fails in its ability to differentiate "self" from "non-self" in the context of immunology. The diseases are intriguing, both clinically and immunologically, for their diversified clinical phenotypes and complex underlying immunological mechanisms. This book offers cutting-edge information on some of the specific autoimmune disease phenotypes, respective diagnostic and prognostic measures, classical and new therapeutic options currently available, pathogenesis and underlying mechanisms potentially involved, and beyond. In the form of Open Access, such information is made freely available to clinicians, basic scientists and many others who will be interested regarding current advances in the areas. Its potential readers will find many of the chapters containing in-depth analysis, interesting discussions and various thought-provoking novel ideas.

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