

Macrophage Activated Syndrome associated with Adult Onset Still Disease

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ABSTRACT

Haemophagocytic lymphohistiocytosis (HLH) is an underrecognized hyperinflammatory condition with a high mortality, characterized by inappropriate survival of histiocytes and cytotoxic T cells (CTLs), leading to a cytokine storm, haemophagocytosis and multi-organ damage (1). The currently accepted terminology includes two forms of HLH: the primary or familial HLH (fHLH) and the secondary HLH (sHLH) (2). The sHLH associated with rheumatic conditions is known as macrophage activation syndrome (MAS). MAS can develop at any time during the evolution of the rheumatic diseases: at the beginning, during flare of the disease or during intercurrent infections – mostly with viral trigger. We present a case of MAS in an patient with adult-onset Still Disease. It is of great importance to be recognized in early stages, because if promptly treated it might respond well to combination therapy of glucocorticoids and IL1- blockers.

Keywords: Haemophagocytic lymphohistiocytosis, Adult Onset Still Disease, macrophage activation syndrome

INTRODUCTION

A 72-year-old woman addressed the clinic for generalized fatigue with recurrent febrile episodes accompanied by chills (38-39°C), arthralgias of the small joints of the hands and knees, low back pain, symptoms with onset of more than 14 days.

She had medical history of arterial hypertension (2010), type 2 diabetes mellitus (2018) and adult-onset Still's disease (AOSD) treated with methotrexate (20 mg/week) and prednisone (10 mg/day). Her AOSD began in April 2018 with recurrent fever and arthritis of the small joints of the hands, accompanied by leukocytosis and intense inflammatory syndrome, with very high titers of ferritin (16192 ng/mL - normal range: 4.63-204 ng/mL). Abdominal computed tomography (CT) had revealed splenomegaly. The patient was diagnosed then with AOSD according to Yamaguchi's criteria after exclusion of infectious causes, malignancy and other inflammatory rheumatic diseases (negative immunology for rheumatic factor, anti-citrullinated protein antibodies, antinuclear antibodies). The patient initially

received glucocorticoids, which were discontinued after 6 months, in combination with methotrexate in doses that gradually increased up to 20 mg/week, the dose she had been receiving for the past 2 years prior admission.

On admission, clinical examination revealed tachycardia (120 beats per minute), fever (38.6° C) and tenderness of wrists, right second and forth metacarpophalangeal joints and knees, without rash or palpable lymphadenopathy. Initial basic workup revealed increased inflammatory markers (erythrocyte sedimentation rate of 81 mm/h and C-reactive protein of 199.5 mg/L, normal range 0-5 mg/L), anemia, neutrophilic leukocytosis and reactive thrombocytosis. Laboratory tests also showed negative results for urine cultures and two blood cultures, slightly increased procalcitonin (0.129 ng/mL, range 0.1-0.25 ng/mL meaning unlikely bacterial infection) and extremely elevated ferritin (9232 ng/mL, normal range 4.63-204 ng/mL). Treatment with intravenous methylprednisolone (500 mg/day for 3 days) was followed by oral methylprednisolone

TABLE 1. Laboratory tests within the first two weeks of admission

	day 0	day 2	day 9	day 10	day 12	day 13	normal range
WBC	19.1	25.5	12.4	15.0	15.0	15,7	4 - 10/mL
PLT	597	539	575	546	253	108	150 - 400/mL
HB	10.0	9,3	8,8	9.8			11 - 15 g/dL
CRP	199.50	234	72.7	126.3	185.5	187	0 - 5 mg/L
ESR	81		99			54	2 - 20 mm/h
proC	0.129	0.261		0.304	5.470	-	-
ferritin	9232	8609	-	-	-	-	4.63-204 ng/mL
FBN	-	-	-	1.53	-	-	1.7-4.2 g/L
LDH	-	-	-	-	1548	3681	125 - 220 U/L
ALT	35	-	-	-	-63	149	63 0 - 55 U/L
AST	33	-	-	-	202	552	202 5 - 34 U/L
CR	0.6	-	-	-	0,73	2,52	0.57-1.11 mg/dL

Abbreviations: CR – serum creatinine; FBN – fibrinogen; HB – hemoglobin; PLT – platelet count; proC- procalcitonin; WBC – white blood cell count

TABLE 2. Laboratory tests within the first week after rituximab

	day 18 before rituximab	day 22	day 23	day 24 the 6th day after rituximab	normal range
WBC	10200	1460	500	10800	4-10/ μ L
PLT	16000	25000	41000	205000	150-400/ μ L
HG	5.7	8.2	8.3	8,8	11-15 g/dL
CRP	105	49	-	25	0-5 mg/L
ESR	20	-	-	0.81	2-20 mm/h
CR	5.69	-	2,38	0.81	0.57-1.11 mg/dL

Abbreviations: CR – serum creatinine; CRP – C-reactive protein; HB – hemoglobin; PLT – platelet count; WBC – white blood cell count

lone (64 mg/day, representing 1 mg/kg/day) with a combination of empirical antibiotics (intravenous ceftriaxone, 2 g/day for 7 days, and oral ciprofloxacin, 1 g/day for 7 days). Whole body CT was performed which reconfirmed splenomegaly and detected multiple mediastinal, axillary, abdominal lymphadenopathies, without visible focused processes. The dynamics of blood parameters are illustrated in Table 1.

Because of sudden and rapid decrease in platelets count, a peripheral smear and bone marrow biopsy were performed which showed rich cellular red marrow, normal maturation on all series, with a reactive global appearance. The patient's state rapidly deteriorated: creatinine decreased to 6 mg/dL, hemoglobin dropped to 5.4 g/dL, severe thrombocytopenia appeared (26000/mm³), while ferritin levels rose to 140000 ng/mL (normal range 4.63-204 ng/mL) and procalcitonin to 10 ng/mL despite treatment with broad spectrum antibiotics (linezolid and meronem), dexamethasone (16 mg/day) and transfusions with erythrocytes, fresh frozen plasma and

platelets. The patient was transferred to a nephrology clinic. Strong suspicion of macrophage activation syndrome (MAS; HScore = 187 - probability of secondary hemophagocytic lymphohistiocytosis) indicated a new biopsy, which was performed at the level of the iliac crest and which showed very rare megakaryocytes, frequent active macrophages and some hemophagocytes (Figure 1). Transfusions and antibiotic treatments (meronem and vancomycin) were continued and rituximab (500 mg) and etoposide (50 mg, 2 doses) were added. After an initial decrease in the number of leukocytes to 500/ μ L, which was explained in the context of rituximab administration, the patient's evolution was progressively favorable (Table 2). The patient was discharged with an improved general condition, with normal values of leukocytes and platelets and was recommended treatment with oral methylprednisolone (8 mg/day) and subcutaneous methotrexate (10 mg/week). Unfortunately, 4 weeks after the patient's discharge, the family reported the patient's death, preceded by a relatively sudden neurological degradation.

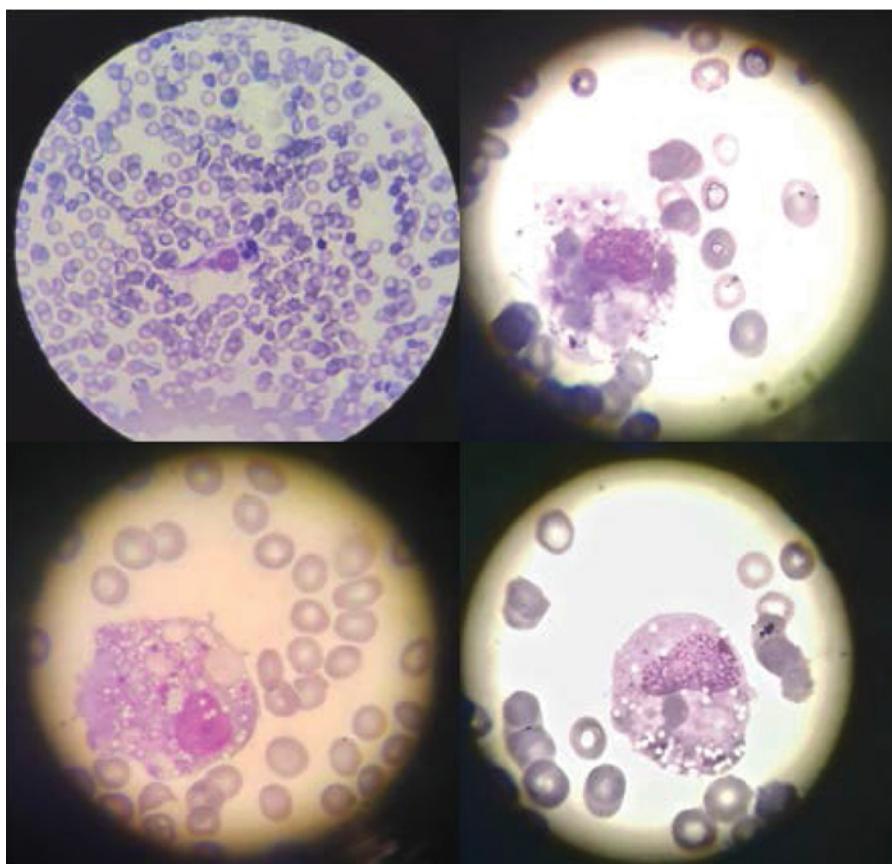


FIGURE 1. Bone marrow cells; May-Grunwald Giemsa staining; details of medullary smear with a vacuole-activated macrophage that phagocytoses red blood cell precursors (material provided courtesy of Dr. Stefan Gabriel; “Dr. Carol Davila” Clinical Nephrology Hospital)

DISCUSSION

Haemophagocytic lymphohistiocytosis (HLH) is an underrecognized hyperinflammatory condition with a high mortality, characterized by inappropriate survival of histiocytes and cytotoxic T cells (CTLs), leading to a cytokine storm, haemophagocytosis and multi-organ damage (1).

TERMINOLOGY

The currently accepted terminology includes two forms of HLH: the primary or familial HLH (fHLH) and the secondary HLH (sHLH) (2). The term primary HLH refers to an underlying genetic abnormality, with the developing of a severe form of cytokine storm syndrome occurring in infancy, typically within the first few days to months of life. The fHLH is a result of homozygous, or compound heterozygous, mutations in genes involved in the perforin-mediated pathway of cytolysis shared by natural killer (NK) cells (innate immunity) and cytotoxic CD8 T cells (adaptive immunity) (3). The secondary HLH indicates that the disorder is secondary to underlying conditions such as infection, autoimmune/rheumatologic, malignant, or metabolic conditions (4). The sHLH associated with rheumatic conditions (especially systemic juvenile idiopathic arthritis – sJIA or its adult correspondent form – adult onset Still Disease - AOSD) is known as macrophage activation syndrome (MAS).

HISTORY

The first description of the disease belongs to Scott and Robb-Smith in 1939 being called “histiocytic medullary reticulosis” (5). In 1952, the familial form of HLH, was presented by Farquhar and Claireaux (6). Later on, Risdall mentioned for the first time a viral association with HLH and proposed that the condition be called virus-associated HLH (7). The term of MAS was used first in 1993. Since these historical data, researchers have documented the wide clinical range of this disease and the fact that infection often triggers both primary and secondary HLH.

Besides MAS, which is associated with autoimmune/autoinflammatory rheumatic conditions, secondary HLH is associated with viral infections (Epstein-Barr Virus, Cytomegalovirus, Parvovirus B-19, Herpes Simplex Virus, HIV, novel coronavirus), malignancies (leukaemia, lymphoma) or others conditions (tuberculosis, malaria, enteric fever, leishmaniasis) (8).

MODE OF DEVELOPING

Regardless of cause, physiologically, HLH is characterized by defective CTLs function (activation and proliferation of T lymphocytes - mainly CD8+cytotoxic T cells and NK cells) coupled with unbridled macrophage activity (over-activation and proliferation of macrophages followed by phagocytosis of

bone marrow hematopoietic cells and/or reticuloendothelial system cells in other organs), leading to excessive cytokine production – cytokine storm – (including interferon-gamma (IFN- γ), interleukin (IL)-1, IL-6, IL-18, and tumor necrosis factor-alpha (TNF α), subsequent immune dysregulation, and tissue damage (4, 8). A key clinical feature of sHLH is hyperferritinaemia, which is induced by the milieu of cytokines present in MAS/sHLH leading to upregulation of ferritin synthesis and is itself capable of inducing NF- κ B and promoting a pro-inflammatory state (9, 10, 11).

CLINICAL AND LABORATORY PARAMETERS

sHLH/MAS is a clinical syndrome with features that overlap with and mimic the symptoms and signs of other systemic illnesses such as sepsis, malignancy and an active rheumatic disease. There are no agreed diagnostic criteria to date for sHLH/MAS, but it should be considered in an unwell, feverish patient in certain at-risk populations (2).

Fever is the dominant symptom, with transition from fever-spikes to permanent, non-remitting fever or aggravated fever during treatment for an infection. Other symptoms, that may occur in sHLH/MAS include: liver and spleen enlargement, skin rash, adenopathy; neurological dysfunction (poor prognostic marker) it can occur early in the disease course, as in established disease, varying from subtle changes in mood and personality, to seizures, limb weakness, cranial nerve palsy, reduced conscious level and coma (12, 13); acute kidney injury, which may be present in up to 62%, of whom 59% require renal replacement therapy, and approximately one-third of the patients who survive have chronic kidney disease at 6 months (14); pulmonary involvement (poor prognostic factor) is found in approximately half of sHLH patients and may present as acute respiratory distress requiring mechanical ventilation (15).

Hyperferritinaemia (extreme high levels) is a cardinal feature of the laboratory parameters, with levels > 10000 mg/l being highly sensitive and specific (16); ferritin levels correlate with disease activity and prognosis: a decline of less than 50% of the initial value after treatment is associated with higher mortality rate (17). Other laboratory tests with good sensitivity and specificity in sHLH/MAS are: increased lactate dehydrogenase level (in the context of multiple organ damage), hypertriglyceridemia (due to low lipoprotein lipase activity in context of high TNF α levels) and hypo-fibrinogenemia; decrease in platelets count, or other cytopenia, transaminitis, high levels of C reactive protein discrepant over falling ESR (due to low fibrinogen levels) (2, 18). An important consideration is related to the absence of liver functions tests abnormality,

which should prompt to consider other diagnosis (18).

Due to lack of the unique clinical, biological or histological feature, a very important consideration of the laboratory parameters consists in repeatedly evaluation of these tests during evolution.

Some authors mentioned that could be difficult to distinguish between “Hyperferritinemic Syndrome”: MAS, AOSD, septic shock and catastrophic antiphospholipid syndrome which share common clinical and pathogenic features. This concept of hyperferritinemia as a major contributor in the pathogenesis of these conditions may be extremely important in considering more targeted therapy. It is to be hoped that busy clinicians may appreciate the value of ferritin measurements when managing critically ill patients and that these assays may be useful in guiding therapy and predicting prognosis (21).

The presence or the amount of hemophagocytosis in aspirate or the core biopsy specimen do not correlate with disease probability, nor with fever or ferritin levels, and it is not mandatory for the diagnosis of sHLH/MAS, as it is a late feature during disease evolution (18).

MAS AND RHEUMATIC CONDITIONS

MAS can develop at any time during the evolution of the rheumatic diseases: at the beginning, during flare of the disease or during intercurrent infections – mostly with viral trigger. The prevalence of MAS in rheumatic conditions vary across reports: sJIA (10%), AOSD (10-15%), systemic lupus erythematosus (0.9 -9%) - during first stage of reactivation / miscarriage or after birth, dermatomyositis, systemic sclerosis, antiphospholipid syndrome, mixed connective tissue disease, Sjogren syndrome, vasculitis, spondylarthritis, rheumatoid arthritis, sarcoidosis (2,8,19,20).

DIAGNOSTIC PROBABILITY FOR sHLH/MAS

The reactive (secondary) hemophagocytic syndrome diagnostic score, called the HScore, was developed in 2014 and can be used to estimate an individual's risk of having sHLH. This scoring system is freely available online (<http://saintantoine.aphp.fr/score/>) (22). HScore consists of nine variables distributed in clinical domain (known underlying immunosuppression, high temperature, organomegaly), biological domain (level of triglyceride, ferritin, serum transaminase, fibrinogen, cytopenia) and cytologic domain (hemophagocytosis features on bone marrow aspirate). Each variable corresponds to a number of points (starting from 0 = feature absent), HScore being the sum of all points. The probability of having hemophagocytic syndrome ranged from

<1% with an HScore of ≤ 90 points to >99% with an HScore of ≥ 250 points. A cut off level of 190.5 points corresponds to a sensitivity of 96.7% and a specificity of 98.4 for probability of sHLH (22).

PROGNOSTIC

HLH is a severe disease, with potentially fatal evolution, especially when the diagnosis is delayed. The mortality rate is high, in sHLH of any cause in adults has been reported in 41%. sHLH/MAS associated with autoimmune diseases has a range of mortality between 5-39%, depending of the recognition of the disease and the underlying condition of immunosuppression. In sHLH associated with EBV the mortality rate has a direct relationship with hypoalbuminemia, hyperbilirubinemia and the LDH serum level. The highest mortality rate has been reported for sHLH associated with malignant conditions, where it ranges from 42 to 88%. The mortality associated with HLH is increased in older age and in the presence of comorbidities, regardless of the causative agent (23,24,25).

MANAGEMENT OF HLH

Broadly, treatment of HLH involves immune-suppressive and modulatory agents, biological response modifiers, treatment of the inciting illness if secondary, and subsequent stem-cell transplantation. Therapy is aimed at suppressing the hyperinflammatory state and immune dysregulation that leads to life-threatening organ damage and susceptibility to deadly infections (4).

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MAS is rather unique in that these sHLH forms may respond quite well to high dose corticosteroids alone (immediate treatment with IV methylprednisolone 1 gram daily for 3-5 days) plus IVIg (1gram/kg daily for 2 days – repeat in 14 days). Cyclosporin (CSA) (2-7mg/ kg/day) therapy has also become a prominent therapy in addition to corticosteroids in MAS, as CSA may preferentially inhibit lymphocytes by targeting transcription factors that activate various cytokine genes (26). CSA likely inhibits the cytokine storm of MAS and has a role to prevent recurrent episodes. Cyclophosphamide has also been used to target lymphocytes in MAS (27). Second-line treatment in clinical deterioration despite immediate treatment uses Anakinra (1-2 mg/kg, increasing to maximum 8mg/kg/day). As third-line treatment for refractory cases can be used Etoposide regimens (150mg/m² twice weekly for 2 weeks followed by 150mg/m² once weekly for six weeks), but the risks must be weighed carefully and discussed with the haematologist (2,4).

Other treatment considerations targeted antibiotics to treat infectious triggers, for EBV Rituximab may be considered and in malignancy cases cancer targeted chemotherapy (2).

CONCLUSION

sHLH is still underrecognized and has a high mortality rate. Usually, it is triggered by an infectious factor (commonly a viral agent), but also other factors (autoimmunity, autoinflammation, malignancy). Promptly treated it might respond well to combination therapy of glucocorticoids and IL1-blockers.

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