EXTENDED REPORT

Reactive haemophagocytic syndrome in adult-onset Still's disease: a report of six patients and a review of the literature

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Objective: To examine the prevalence and characteristics of patients with reactive haemophagocytic syndrome (RHS) complicating adult-onset Still's disease (AOSD).
Methods: Of 50 patients with AOSD fulfilling Yamaguchi and Fautrel criteria followed in our department, clinical and laboratory data, course and treatment of six patients with histologically proven RHS and without any obvious cause other than AOSD were retrospectively recorded.
Results: RHS led to AOSD in two cases, whereas it appeared after a mean duration of 3.5 years from onset of AOSD in the other cases. The main symptoms were fever (n = 6), polyarthralgias or myalgias (n = 4), lymphadenopathy or splenomegaly (n = 3), pharyngitis (n = 3), rash (n = 3), pleuritis (n = 3), hepatomegaly (n = 1), normal or low leucocyte count (n = 4), anaemia (n = 6), lymphocytopenia (n = 6), thrombocytopenia (n = 4), hyperbasophilic lymphocytes (n = 2), abnormal liver function tests (n = 6) and increased serum triglyceride level (n = 6). Serum ferritin concentration was constantly increased (>10 000 μg/l in five cases, with <5–35% in glycosylated form). Two patients presented with coagulopathy. Treatment comprised corticosteroids (n = 4) and intravenous immunoglobulins (n = 3), whereas prednisone was unchanged in one case. One death due to pneumonia occurred 15 days after RHS. With a follow-up ranging from 2 to 7.5 years, the other patients were in remission with prednisone plus etanercept (n = 1), prednisone plus methotrexate (n = 1), low-dose prednisone (n = 2) or without treatment (n = 1).
Conclusion: RHS is not uncommon in AOSD. It should be evoked in a patient with AOSD in the absence of hyperleucocytosis, thrombocytopenia, lymphopenia and coagulopathy, or in the presence of high serum ferritin and triglyceride levels.

Haemophagocytic syndrome is a rare but potentially fatal condition, which is characterised by acute fever, hepatosplenomegaly, lymphadenopathy, pancytopenia, and raised levels of serum ferritin, triglycerides and liver enzymes. It may be caused by activation and uncontrolled non-malignant proliferation of T lymphocytes and macrophages, which lead to phagocytosis of haematopoietic cells in various organs, and by overproduction of cytokines.[1–3] It can be primary or familial—essentially in childhood—or secondary (reactive), related to various situations such as infections, malignancies, drugs (uncommonly) or systemic diseases.[2–4] When it is secondary, it appears to belong to a spectrum ranging from infection occurring mostly in inactive systemic diseases treated with immunosuppressive treatment to systemic disease-specific manifestation occurring during flare. Systemic lupus erythematosus and Still's disease seem to be the main systemic diseases according to the definition of specific reactive haemophagocytic syndrome (RHS).[3–7] RHS is recognised by paediatricians as the most severe complication of systemic onset juvenile idiopathic arthritis (SOJIA)—also named childhood Still's disease[7 8]—but this complication was poorly studied in adult-onset Still's disease (AOSD). RHS and AOSD share several clinical and laboratory features, including high fever, hepatosplenomegaly, lymphadenopathy, liver injury, hyperferritinaemia and coagulopathy, which may explain the difficulty in recognising RHS complicating the flare of AOSD. The main difference between the two diseases is cutaneous and articular involvement, which is present in more than 80% of AOSD and is uncommon in RHS.[1 3 9 10] Most of the previous articles about AOSD-associated RHS were case reports. Hence, the course and treatment of RHS occurring in AOSD are not clearly described. The objective of this study was to analyse retrospectively a series of six patients with RHS complicating AOSD and to compare their characteristics with those of 10 previously reported cases in the literature. This is the largest series of this complication reported to date.

PATIENTS AND METHODS

Patients

We reviewed retrospectively the charts of six patients with AOSD (occurring at over 16 years of age) complicated with RHS and followed from 1985 to 2003 in our department of internal medicine. All patients fulfilled both Yamagushi[11] and Fautrel[12] criteria, considered to be the most sensitive and specific criteria for the diagnosis of AOSD, after exclusion of infectious disease, malignancy or auto-immune disease. Because consensual diagnosis criteria for RHS in adulthood are not available,[13] only patients with cytologically or histologically proven RHS were included—that is, those showing the presence of macrophages without notable cytological abnormalities, presenting abnormal signs of active haemophagocytosis affecting red cells, platelets, or polymorphonuclear leucocytes or lymphocytes. One patient was previously reported without details elsewhere.[4]

Abbreviations: AOSD, adult-onset Still's disease; ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulopathy; IVIG, intravenous immunoglobulin; RHS, reactive haemophagocytic syndrome; SOJIA, systemic onset juvenile idiopathic arthritis; TNFα, tumour necrosis factor α

Clinical and laboratory data, course and treatment were recorded. Data collected included age at onset of Still's disease and at diagnosis of RHS, sex, country of origin, medical history, and clinical and laboratory features at the time of diagnosis of RHS. Cutaneous rash was defined as transient maculo-papular lesions and acute respiratory distress syndrome (ARDS) caused by acute dyspnoea associated with widespread pulmonary opacities. Laboratory tests included blood cell count, determination of serum ferritin level before transfusion of platelets or red blood cells, liver function tests, determination of lactate dehydrogenase level, haemostasis tests, determination of C reactive protein, erythrocyte sedimentation rate and serum triglyceride level. Disseminated intravascular coagulopathy (DIC) was defined as prolonged prothrombin time, hypofibrinogenaemia or increased fibrinogen degradation products.

Literature review

The available literature in English was reviewed for cases of RHS reported as a specific complication of AOSD. The Medline database was searched using a strategy that included the following medical subject headings: ''hemophagocytosis'', ''hemophagocytic syndrome'', ''hemophagocytic lymphohistiocytosis'' or ''macrophage activating or activated or activation syndrome''; the subset heading was ''adult-onset Still's disease''. All articles were searched in Medline until August 2005. Cases were excluded if (1) patients were <16 years old or had SOJIA persisting in adulthood; (2) cytological or histological confirmation of haemophagocytic syndrome was lacking; (3) they showed evidence of any other known underlying cause of RHS; or (4) the description of cases was insufficient. Hence, 10 cases were analysed similar to our 6 cases.

Statistical analysis

Descriptive statistical analysis was carried out using Fisher's exact test and Wilcoxon's test.

RESULTS

Between 1985 and 2003, AOSD was diagnosed in 50 patients in our tertiary referral centre, yielding a prevalence of 12% of RHS. Tables 1 and 2 summarise the clinical and laboratory data of the six patients.

Clinical characteristics

Of the six patients whose data were recorded, there were four women and two men from sub-Saharan Africa (n = 3) and Europe (n = 3). Median age at RHS diagnosis was 43 (range 22–72) years. The medical history of patients was uneventful except for patient no 4, who had a history of vitiligo, atopy, diabetes mellitus and bullous pemphigoid. RHS inaugurated AOSD in two cases (no 2 and 6). In patient no 5, RHS occurred 1 month after the onset of Still's disease, when she was in remission after a short course of prednisone and non-steroidal anti-inflammatory drugs. In three patients, RHS appeared during the course of AOSD after 2, 4.5 and 7.5 years, respectively, after the onset, although two of them (no 1 and 3) received 0.4 mg/kg daily prednisone a few months before. In two cases (no 3 and 6), gold salts and anti-tuberculosis agents may have been possible triggering factors because they were introduced just before the onset of RHS, which improved once the drugs were withdrawn.

At the onset of RHS, all patients had acute and high spiking fever associated with various symptoms: rash, arthralgias or myalgias, sore throat, lymphadenopathy and hepatosplenomegaly (table 2). Pleuritis was present in half the patients, and was disclosed by pain (no 5), pleural rub (no 4) or dry cough (no 6). Patients no 1 and 6 developed an ARDS.

Laboratory features

The most frequent laboratory features were anaemia, which was normocytic in half the patients, lymphopenia, marked increased C reactive protein, and raised levels of serum ferritin, triglycerides and aminotransferases (table 2). Normal or low leucocyte count and thrombocytopenia were observed in four of six patients. Hyperbasophilic lymphocytes were present in peripheral blood smears in patients no 1 and 4. Serum ferritin was constantly increased, with mean levels of 56 190 and >10 000 μg/l in five patients. Its glycosylated form was <20% in five out of six patients. Triglyceride concentrations were constantly increased and were >3 mmol/l in four of six patients. DIC was present in two patients (no 1 and 6). ANAs were present in patients no 2 and 6 at low titre, without specificity. Rheumatoid factor was positive in patient no 6. Albumin was <30 g/l tested in all four patients without proteinuria, and was probably related to the marked inflammation. Serum creatinine and creatine phosphokinase levels were normal.

Bone marrow aspirate, performed in five patients, showed phagocytosis of various haematopoietic cells by histiocytes, whereas this phenomenon was not identified in bone marrow biopsy in four patients. Haemophagocytosis was evidenced by bone marrow biopsy in only patient no 6, who did not have a bone marrow aspirate.

Treatment and outcome

One patient (no 1) died suddenly after fibreoptic bronchoscopy, a day after his admission to the intensive care unit for an ARDS, and 15 days after the onset of RHS, although steroids and intravenous immunoglobulin (IVIG) induced a good response. Autopsy examination displayed pneumonitis of non-infectious origin (infiltration of alveoli with lymphocytes and macrophages without signs of haemophagocytosis or malignancy and with no infectious agents).

In the other patients, the mean delay between institution of treatment and remission was 20 days (range 4–45 days). Treatment consisted of corticosteroids in four patients, alone (prednisone 0.5 mg/kg daily for patient no 4 and methylprednisolone pulses 15 mg/kg daily for 3 days, followed by 1 mg/kg daily prednisone for patient no 6) or with methylprednisolone pulse followed by prednisone in association with IVIG (total dose 2 g/kg given over 2–5 days, patients no 1 and 2). IVIG was used alone in patient no 5. The prednisone dose was not modified in patient no 3, in whom remission was observed after withdrawal of gold salts and institution of granulocyte cell stem factor. In patient no 6, mechanical ventilation and adrenergic drugs were necessary to treat ARDS and cytokinic shock before starting methylprednisolone pulses.

In the five surviving patients, the mean follow-up from RHS was 4.7 (range 2–7.5) years. AOSD remained self-limited in patient no 6, whereas patients no 4 and 5 had intermittent flares and patients no 2 and 3 had a chronic course. Relapse of RHS was never observed, but a bone marrow aspirate was not repeated. At the last visit, all patients were in remission, without treatment (n = 1), with low-dose prednisone (n = 2), or with a combination of prednisone and etanercept (n = 1) or of methotrexate and prednisone (n = 1).

Comparison of the characteristics of our patients with those from the literature

We were able to identify 27 cases of histologically proven RHS complicating AOSD[4 5 14–28] in the global literature. The patients were from Europe (n = 14), Japan (n = 11) and Korea (n = 2). Of these 27 cases, we excluded 17 cases in which RHS was concomitant with infection[4 5 15 17 28] those which were not published in the English language[6 20–22 25] or were not well

Table 1 Clinical features and laboratory findings of each of the six patients with adult-onset Still's disease and reactive haemophagocytic syndrome

	Case no 1	Case no 2	Case no 3	Case no 4	Case no 5	Case no 6
Sex/age at onset of RHS	F/38 y	F/22 y	M/44.5 y	M/72 y	F/47 y	F/36 y
AOSD duration before RHS	2 y	0	7.5 y	4.5 y	1 mo	1 mo
Previous IS therapy	CS	−	CS	−	−	−
Clinical findings						
Fever >39°C	+	+	+	+	+	+
Rash	−	+	+	−	+	−
Arthralgia	−	+	+	−	−	+
Myalgia	−	+	+	−	+	−
Sore throat	−	+	−	+	+	−
Lymphadenopathy	−	+	−	−	−	+
Splenomegaly	+	−	−	−	−	+
Hepatomegaly	−	−	−	−	−	+
Pleuritis	−	−	−	+	+	+
ARDS	+	−	−	−	−	+
Biochemistry						
Haemoglobin (g/l)	119	87	93	110	94	59
Leucocyte (counts/mm^3)	6800	27,600	2700	4500	13730	1,470
PMN count/mm^3	3800	25000	1100	3250	10280	830
Lymphocyte count/mm^3	923	1400	860	540	1250	500
Platelet count/mm^3	25000	352000	98000	60000	560000	17000
Hyperbasophilic form	30%	—	23%	—	—	—
ALT/AST, U/l (<20/41)*	3420/1630	37/60	33/56	38/61	52/18	51/127
LDH, U/l (<280)*	3600	1000	550	740	350	3026
Ferritin, µg/l (15–300)*	210000	11470	71600	17440	645	26000
Glycosylated ferritin (>50%)*	35%	<5%	ND	<5%	10%	6%
Triglycerides, mmol/l (<1.6)*	3.27	1.9	3.64	1.76	3.85	4.24
ESR, mm/h	14	80	ND	50	116	70
CRP, mg/l (<5)*	214	355	39	393	259	154
DIC	+	−	−	−	−	+
ANA	−	1:320	−	−	−	1:80
Possible target agent	−	−	Gold salts	−	−	ATB
Treatment	High-dose CS, IVIG	High-dose CS, MTX, IVIG	G-CSF stop gold salts	CS	IVIG	Resuscitation for overwhelming shock and DIC high-dose CS stop ATB
Outcome	Death	Remission (within 1.5 mo)	Remission (10 d)	Remission (4 d)	Remission (20 d)	Remission (10 d)

ANA, antinuclear antibodies; AOSD, adult-onset Still's disease; ARDS, acute respiratory distress syndrome; ATB, anti-tuberculosis treatment; CRP, C-reactive protein; CS, corticosteroids; d, days; DIC, disseminated intravascular coagulopathy; ESR, erythrocyte sedimentation rate; G-CSF, granulocyte cell stem factor; IS, immunosuppressive; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; mo, months; MTX, methotrexate; ND, not determined; PMN, polymorphonuclear neutrophil; RHS, reactive haemophagocytic syndrome; y, years; −, finding was absent; +, finding was present; .
*Reference ranges for normal values of biological parameters are indicated in parentheses.

described.[6 4 14 17 24] Table 2 summarises the characteristics of the 10 remaining cases with AOSD-related RHS.

The characteristics of our six patients appeared similar to those reported in the literature. Female patients were more often affected, but had the same sex ratio (1:2) as the patients with AOSD without RHS.[9] A simultaneous diagnosis of AOSD and RHS was common and patients in whom RHS occurred during the course of AOSD did not show heavy immunosuppression. In patients no 3 and 6, the administration of gold salts and antituberculosis drugs may have been the precipitating factors of RHS. Takeshita[26] also suggested that penicillin G might be the triggering factor for RHS in his case.

Pleuritis and ARDS are atypical findings in AOSD, whereas they were present in more than one third of patients who had RHS complicating AOSD. The other clinical features observed during RHS were indistinguishable from those of flare of AOSD.

Two uncommon laboratory features for AOSD were present in cases of RHS: thrombocytopenia or normal or low leucocyte count was present in 4 of 6 patients and in 8 of 10 patients in the literature. Hyperbasophilic lymphocytes were not reported in patients in the literature. A very high serum ferritin level (>10 000 µg/l) was observed in 5 of 6 of our patients and in 8 of 10 patients in the literature. The mean ferritin level was 56 190 µg/l in our patients (median: 21 720 µg/l) and 61 560 µg/l (median: 32 157 µg/l) in the 10 patients in the literature. DIC was observed in 2 of our six patients (patients 1 and 6) and in one third of patients with AOSD-related RHS in the literature.[18 20] It was associated with severe liver cytolysis with aminotransferases >8 N in 3 of 4 tested patients (patient 1[18 26]). Half the patients with DIC died (patient 1)[26] or required mechanical ventilation (patients 1 and 6).

Various drugs were used in the literature: IVIG alone[6] or a combination of steroids and other immunosuppressants such as cyclophosphamide,[23] etoposide[23] and ciclosporin A.[18] Two patients died: one died of massive intestinal haemorrhage secondary to DIC,[26] and the cause of death of the other was not stated.[5] In the other patients, the long-term course was not reported.

DISCUSSION

Our series, in which prevalence of RHS is 12%, represents the largest experience to date with RHS in AOSD. It should, however, be borne in mind that this complication was not

Table 2 Characteristics of patients with adult-onset Still's disease (AOSD) with reactive haemophagocytic syndrome (RHS) in our series compared with those of the literature, and with patients with AOSD without RHS reviewed by Pouchot[9]

	Series of patients with AOSD with RHS		Cases of AOSD with RHS from the literature[5 19 20 25 28]		Review of patients with AOSD without RHS[9]	
	n=6	%	n=10	%	n=659	%
Median age (years) and range	42.9 (22–72)		44.7 (19–69)		ND	
Sex ratio (M:F)	2:4		3:7		216: 443	
Simultaneous AOSD and RHS*	2		4/5		–	
AOSD duration before RHS**	41 months		1 month		–	
Underlying IS treatment	2		1/5		–	
Possible drug induction	2		1/5		–	
Death	1		2		19	
Clinical features						
Fever>39°C	6	100	10	100	544/574	94.8
Rash	3	50	10	100	537/650	82.6
Arthralgias or myalgias	3	50	8	80	655	99.4
Sore throat	3	50	6	60	379/575	65.9
Lymph node or splenomegaly	3	50	6	60	346/558	62
Hepatomegaly	1	16.6	2/5	40	190/493	38.5
Pleuritis	3	50	2/6	33.3	145/618	23.5
Acute respiratory distress	2	33.3	2/6	33.3	ND	ND
Laboratory features						
Anaemia	6	100	9	90	267/410	65.1
Thrombocytopenia	4	66.6	8/9	88.8	ND	ND
Normal leucocyte count or leucopenia	4	66.6	7	70	51/602	8.5
Leucocytosis>15 000/mm^3	1	16.6	2	20	313/517	60.5
Lymphopenia	6	100	3/4	75	ND	ND
Ferritin>10,000 µg/l	5	83.3	8	80	ND	ND
Glycosylated ferritin<20%	4/5	80	ND	ND	ND	ND
Raised triglyceride level	6	100	ND	ND	ND	ND
Raised serum aminotransferase level	6	100	4/5	80	375/564	66.5
Raised LDH	6	100	7/7	100	ND	ND
Albumin<30 g/l	4/4	100	2/2	100	243/299	78.3
Antinuclear antibodies	2	33.3	1/9	11.1	40/651	6.1
Rheumatoid factor	1	16.6	0	0	28/652	4.3
DIC	2	33.3	2/6	33.3	ND	ND

AOSD, adult-onset Still's disease; DIC, disseminated intravascular coagulopathy; IS, immunosuppressive; LDH, lactate dehydrogenase; RHS, reactive haemophagocytic syndrome.
*RHS was considered simultaneous if diagnosed during the first flare of ASOD, **in patients without simultaneous diagnosis.

systematically searched for in all our patients with AOSD, and weak haemophagocytosis may have been missed by the cytologist. Thus, the actual prevalence may be higher. In another study of 12 bone marrow specimens in patients with AOSD, haemophagocytosis without evidence of viral infection was noted in 2 (16.7%) patients. Clinical features were not reported in this study.[14] No other data on prevalence of RHS in AOSD are available in the literature. The prevalence of RHS of all causes in SOJIA was estimated to be 7%,[8] and approximately 100 cases of RHS complicating SOJIA were reported.[5 7 8 29 30] This suggests that RHS in AOSD is more common than previously recognised in the literature and has probably been underdiagnosed.

In SOJIA, drugs and viruses were indicated as possible triggering factors for RHS. Ten cases of RHS occurred after administration of gold salts, and it was hypothesised that gold retention by macrophages may activate these cells.[7 8] To the best of our knowledge, our case no 3 is the first report with a possible role of gold salts in AOSD. Gold salts should be therefore contraindicated in Still's disease. Also, their efficiency has not been demonstrated.[9]

Our data and literature review showed that RHS could occur at any time during the medical history of AOSD even if a simultaneous diagnosis of AOSD and RHS was common. Flare of AOSD and RHS are clinically indistinguishable, except for a high frequency of pleuritis and ARDS. Biological findings are certainly more sensitive in evoking the diagnosis of RHS during flare of AOSD. Leucopenia or thrombocytopenia is uncommon in AOSD and hence can serve as an alert. High ferritin level is generally observed in AOSD. Nevertheless, the mean serum ferritin level was 4753 µg/l in the largest study of AOSD,[31] as compared with 56 190 µg/l in our patients and 61 560 µg/l in the 10 patients with AOSD-related RHS reported in the literature. A very high serum ferritin concentration (>10 000 µg/l) was present in 13 of 16 (81.25%) patients. Glycosylated ferritin was <20% in four of our five tested patients. This marker is considered as a better diagnostic tool for AOSD than total serum ferritin.[12] It may, however, also be observed in RHS of other origins[32] and so cannot be distinctive. Raised serum triglyceride level is considered to be a good marker of haemophagocytic syndrome,[3] but it was not specifically analysed in flare of AOSD. In our patients, serum triglycerides were markedly raised during the acute phase of RHS and declined rapidly if treatment was successful. It may be useful for RHS diagnosis. DIC is a serious complication shared by both RHS and AOSD, and is associated with high mortality.[3 9] Although it is described in AOSD case reports, we observed DIC in one third of the patients with AOSD-related RHS (no 1, 6, 18 and 26). It was associated with severe liver cytolysis and high mortality. The death of a German patient with AOSD-related RHS was also attributable to DIC, ARDS and hepatic failure.[27] Although mortality is low in patients with AOSD, most deaths are due to DIC or ARDS, often associated with

hepatitis,[5 10 17 18 26] suggesting that some may have been caused by undiagnosed RHS.

The cytological diagnosis of haemophagocytosis is difficult and should be carried out by an experienced cytologist.[3] Bone marrow biopsy, often performed to eliminate infection or neoplasm, is less sensitive than bone marrow aspirate. A bone marrow biopsy was considered to be normal in two thirds of our patients, whereas RHS was demonstrated in the bone marrow aspirate study. Another case with positive bone marrow aspirate and negative bone marrow biopsy for RHS was reported in the literature.[18]

In accordance with our data in adulthood, Ravelli *et al*[30] found that variables with the highest sensitivity and specificity for RHS in SOJIA were platelet count $\leqslant$262 000/mm^3, white blood cells count $\leqslant$4000/mm^3, fibrinogen level $\leqslant$2.5 g/l, raised liver enzymes, serum ferritin level$\geqslant$10 000 µg/l, triglyceride level$\geqslant$1.6 g/l, and bone marrow aspirate showing haemophagocytosis, hepatomegaly and splenomegaly.

Although the features of RHS and AOSD are well characterised, the underlying physiopathology is not well understood. The most consistent immunological abnormality described in patients with primary or secondary haemophagocytic syndrome is impairment of cytotoxic function.[2] Three recent articles have shown, in patients with SOJIA with or without RHS, a reduced number or defective activity of CD8$^+$ lymphocytes and natural killer cells, sometimes associated with reduced expression of perforin and granzyme—two proteins that mediate cytotoxic activity of these cells.[29 34 35] In the study by Grom, one patient with very low natural killer activity and low levels of perforin expression in all cytotoxic cells was 16 years old at the onset of Still's disease and should be considered to have AOSD and not SOJIA. The deficient cytotoxic function may lead to failure to provide complete pathogen destruction and persistent lymphocyte and macrophage activation.[34] Sustained macrophage activation may result in tissue infiltration, production of ferritin and high levels of tumour necrosis factor α (TNFα) and interleukin (IL), IL-6, IL-18, IL-8, observed in flares of AOSD and RHS.[35] Highly activated macrophages are thought to have a key role in the pathogenesis of SOJIA and AOSD.[15 35] Hence, sustained macrophage activation in AOSD may lead to RHS after a sudden intensification of activation, which might be related to a triggering event such as drug administration.

No consensual treatment for RHS in AOSD exists. Most patients in our study and in the literature received corticosteroids, which often induced a dramatic response, even if used as the sole treatment (no 6). Steroids were shown to be effective in both AOSD and RHS.[3 10] A combination of high-dose prednisone and IVIG was only transiently efficient in patient no 1, who relapsed and died a few days later. Patient no 5 was treated with IVIG alone, with success. IVIG were reported to be effective in both RHS and AOSD when started early.[5 37] Emmenegger[5] successfully used IVIG as the sole treatment in five patients with RHS-related AOSD; one patient died. On the basis of increased serum TNFα level in patients with RHS[3] and AOSD,[34] anti-TNFα agents may be proposed in the treatment of AOSD-related RHS but, to our knowledge they have never been used. The condition of one patient, a boy with corticosteroid-resistant RHS complicating SOJIA dramatically improved 24 h after institution of etanercept.[38] On the other hand, Ramanan[39] reported RHS after the initiation of etanercept in a child with SOJIA. Lastly, two children with SOJIA developed an RHS despite etanercept or infliximab.[29] In other respects, the condition of a patient with AOSD and viral-related RHS deteriorated with the use of etanercept.[28]

In our patients, the long-term outcome seemed similar to those of AOSD without RHS, after the ''storm'' has abated.

In conclusion, RHS is a life-threatening and probably underdiagnosed complication of AOSD. In a patient with known or suspected AOSD, the occurrence during a disease flare of leucopenia or thrombocytopenia and extremely high serum ferritin levels should suggest RHS. Bone marrow aspirate examination is the best diagnostic tool. Potential precipitating drugs should be withdrawn. First-line treatment should use high-dose corticosteroids.

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