Refractory adult-onset Still disease complicated by macrophage activation syndrome and acute myocarditis

A case report treated with high doses (8 mg/kg/d) of anakinra

Federico Parisi, MD, Annamaria Paglionico, MD, Valentina Varriano, MD, Gianfranco Ferraccioli, MD[*], Elisa Gremese, MD[*]

Abstract

Rationale: Myocarditis is a rare but potentially fatal complication of Still's disease (about 7% of total cases).

Patient concerns: A 42-year-old woman was admitted to our ward with high-grade fever, rash and polyarthralgia, lasting since 4 weeks and rapidly complicated by MAS and acute heart failure.

Diagnoses: Adult Onset Still's Disease rapidly developping macrophage activation syndrome and disseminated intravascular coagulopathy, further complicated by iperacute myocarditis with cardiac arrest.

Interventions: After failure of conventional therapies (steroids plus cyclosporine and then biological therapy with Anakinra 100 mg/day), the patient was treated with anakinra 100 mg sc 1 fl 4 times a day.

Outcomes: Fast clinical and laboratoristic improvement and subsequent disease remission with complete recovery of cardiac function.

Lessons: This is the first case report in which high doses of Anakinra have been used to treat a refractory AOSD complicated by MAS and myocarditis. In AOSD complicated by life-threatening conditions, probably we need to consider aggressive therapeutic approaches with higher doses of Il-1 receptor blocker to switch off the hyper-inflammation.

Abbreviations: AOSD = adult-onset Still disease, DMARD = disease modifying antirheumatic drug, MAS = macrophage activation syndrome.

Keywords: adult-onset Still disease, anakinra, macrophage activation syndrome, myiocarditis

1. Introduction

Adult-onset Still Disease (AOSD) is a complex autoinflammatory syndrome first described in 1971 by Bywaters.[1] It is a highly heterogeneous disease entity both in its clinical expression and in its outcome profile. The most classic clinical manifestations of AOSD are high spiking fever, evanescent rash, sore throat, polyarthralgia or arthritis, serositis, lymphadenopathy, hepatosplenomegaly, leucocytosis, elevated polymorphonuclear neutrophils count, high erythrocyte sedimentation rate, high serum ferritin, and elevated liver enzymes.

The clinical course of the disease may follow 1 of 3 patterns: a monocyclic systemic course, an intermittent or polycyclic systemic course, and a chronic course that mimics chronic arthritis.[2]

More rarely than in pediatric patients, adults can experience another serious and potentially fatal manifestation: macrophage activation syndrome (MAS), in about 10% of cases.[3]

This condition is caused by an excessive activation and expansion of T lymphocytes and macrophages and its 3 cardinal features are cytopenias, liver dysfunction, and coagulopathy resembling disseminated intravascular coagulation.[4]

Regarding the cytokine cascade, AOSD is considered an interleukin (IL)-1, IL-6, and IL-18-driven disease.[5]

A rare life-threatening complication during AOSD is myocarditis (7% of cases). It may occur early in the course of Still disease, and its prognosis can be rapidly fatal in the absence of early adequate treatment.[6]

The treatment of life-threatening forms that have failed corticosteroids and disease modifying antirheumatic drugs (DMARDs), considers the use of biological therapy (anti-Tumor necrosis factor agents, IL-1 antagonists, IL-6 antagonists).[7–11]

Plasma exchange and intravenous immunoglobulins are other treatment options in refractory AOSD patients.[12] Despite the

* Correspondence: Gianfranco Ferraccioli, Full Professor, Director of the Institute of Rheumatology and Affine Sciences, School of Medicine, Fondazione Policlinico Gemelli, Catholic University of the Sacred Heart, Via Giuseppe Moscati, 31-00168 Rome, Italy (e-mail: gianfranco.ferraccioli@unicatt.it); Elisa Gremese, Institute of Rheumatology and Affine Sciences, School of Medicine, Fondazione Policlinico Gemelli, Catholic University of the Sacred Heart, Via Giuseppe Moscati, 31-00168 Rome, Italy (e-mail: elisa.gremese@unicatt.it).

existence of all these therapies, mortality rate due to MAS remains high (about 10%).

We report here a case of severe MAS and myocarditis complicating an AOSD in a young female, in which supramaximal high dosage of anakinra (8 mg/kg/d) was used, obtaining full clinical and lab response.

2. Case presentation

We report the case of a 42-year-old female (160 cm, 50 kg), who was admitted to our ward with high-grade fever, rash, and polyarthralgia, lasting since 4 weeks and rapidly complicated by MAS and myocarditis.

The patient gave her signed consent to publish the case.

A year before admission, she noticed itchy maculopapular lesions mainly distributed on the upper limbs, abdomen, and trunk, lasting few hours. After a few months, arthralgia appeared in the hands and wrists. The patient began treatment with hydroxychloroquine and prednisone 5 mg/d, with benefit. Subsequently, because of the onset of fever (1 or 2 daily peaks of mean 39 °C) about 4 weeks before hospital admission and the reappearance of maculopapular lesions and arthralgias, the patient was hospitalized to our hospital.

Admitted first to the Infectious Disease Unit, all specific cultures and serology antibody for infectious agents were negative. The autoantibody panel showed antinuclear antibodies positivity (1/160) with an omogeneus pattern. She was discharged with Paracetamol and the diagnosis of undifferentiated arthritis, but about 1 month later, because of the persistence of symptoms and the appearance of polyarthritis, the patient was hospitalzed and admitted to our ward, with the hypothesis of Still disease. At the admission, blood tests showed significant neutrophilic leukocytosis (white blood cell [WBC] count up to 45,190 unit/uL with Neutrophils-N 43,890 unit/uL) with a marked raise in the indices of cholestasis and liver necrosis (Serum Glutamic Pyruvic Transaminase 604 UI/L, alkaline phosphatase 243 UI/L, gGT 316 UI/L), hypertriglyceridemia (544 mg/dL), and hyperferritinemia (13,138 ng/mL), C reactive protein (CRP) 256 mg/L.

The patient underwent to bone marrow biopsy with detection of cellularity almost exclusively made up of elements of myeloid cell lines, erythroid line deflected to the left, istio-macrophage activation notes with hemophagocytosis, 1% to 2% of plasma cell elements.

The clinical profile of our patient was characteristic of AOSD in line with the Yamaguchi criteria (fever >39 °C, arthralgia, rash, leukocytosis, abnormal liver function tests, and hepatomegaly)[13] with a Pouchot score of 4/12 (fever, rash, leukocytosis, and abnormal liver function tests).[14]

In a few days, she developed a progressive reduction of fibrinogen to 77 mg/dL, a sharp increase of D-dimers up to 31,921 ng/mL, antithrombin III consumption down to 59%, with a reduction of platelets-PLT count, down to a minimum peak of 17,200 unit/uL).

According to Fardet criteria for hemophagocytic syndrome,[15] the patient reached a Hscore of 231 points (33 pts for temperature, 50 pts for hyperferritinemia, 64 pts for hypertriglyceridemia, 30 for fibrinogen, 19 pts for raised indices of liver necrosis, 35 pts for MAS elements in the bone marrow biopsy), conferring a probability of having a MAS of 98%.

For these reasons, we diagnosed MAS and disseminated intravascular coagulopathy in Still disease.

Methylprednisolone at a dosage of 125 mg every 6 hours/d and intravenous Cyclosporine 3 mg/kg/d (increased up to 5 mg/kg) were started. With such therapy, we witnessed a resolution of the fever.

At the 5th day, the patient reported a sudden onset of dyspnea. Gas analysis showed a pH of 7.52 with hypoxia (pO2: 56%) and hypocapnia (pCO2: 28%). Computed tomography angiography showed the presence of pericardial effusion and of bilateral pleural effusions and several areas of hyperdensity affecting large parts of both lungs. Myocardial damage indices were high (Troponin T 0.022 ng/mL → 0.032 ng/mL). The echocardiogram showed the presence of a global hypokinesis with severe left ventricular dysfunction [ejection fraction (EF) 25%], leading to diagnose acute myocarditis in Still disease.

Then, anakinra was started at the standard dose (anti-IL1 drug —100 mg/d).

In few hours, we observed a progressive deterioration of the general conditions up to a cardiac arrest, so the patient underwent cardiopulmonary resuscitation, and she was transferred to the subintensive cardiology unit. There, she received inotropic infusion therapy (norepinephrine, dopamine, levosimendan) and was subjected to multiple transfusions of packed red blood cells and plasma. We decided to increase anakinra to 100 mg sc every 6 hours (with the local Ethics Committee approval) and to decrease methylprednisolone to 125 mg iv/d. Moreover, intravenous immunoglobulins were administered (400 mg/kg/d for 5 days). A new echocardiogram made 24 hours later showed an EF 30%, with persistent severe contractile global dysfunction. Once stable, the patient was then transferred back to our ward.

After an initial improvement of clinical and laboratory parameters, we witnessed a progressive pancytopenia (WBC 631 unit/uL, N 326 unit/uL and lymphocytes-L 247 unit/uL; hemoglobin 8.6 g/dL, PLT 40,500 unit/uL), that was attributed to a possible myelotoxicity of anakinra at the dose 100 mg 4 times a day). For that reason, we decided first to reduce, and then to stop it. We also administered Granulocyte-Macrophage Colony-stimulating factor for 4 days, with resolution of neutropenia.

On the 13th day, the patient developed fever (peak 38.2 °C). The systemic inflammatory indices were substantially over limit (CRP 132 mg/L). Procalcitonin taken at fever pitch was indicative of sepsis (4.77 ng/mL). The urinalyses were compatible with urinary infection. Urine and blood cultures were perfomed, and intravenous therapy with piperacillin/tazobactam 4.5 g × 3/d, vancomicin 1 g × 2/d, and fluconazole 400 mg/d was given with immediate response on fever. Both urine and blood cultures resulted positive for *Pseudomonas aeruginosa*, sensitive to piperacillin/tazobactam. The patient then suspended vancomicin and fluconazole and maintained therapy with piperacillin/tazobactam for 14 days, with improvement of the parameters of inflammation.

During the hospital stay, in consideration of a further deterioration of the blood cell count parameters indicative of a relapse of Still disease (WBC with up to 45,000 unit/uL and ferritin over 16,500 ng/mL), therapy with anakinra 100 mg sc/d and cyclosporine 150 mg/d were given with a gradual slow improvement of blood count and liver parameters.

A second cycle of immunoglobulin 400 mg/kg/d for 5 days, well tolerated, was given.

The last echocardiographic control showed a full recovery of global and segmental kinesis with an EF 65%. She was then discharged.

In the following days, the WBCs and ferritin levels progressively returned to normal values. One month later, we again hospitalized the patient, and a third cycle of intravenous immunoglobulin was administered. Given the stability of the clinical picture, then we started tapering the corticosteroid therapy while maintaining cyclosporine 150 mg/d and anakinra 100 mg 1 fl/d.

At 1-year follow-up, the patient is in good clinical conditions. She is continuing anakinra 1 fl/d and cyclosporine 150 mg/d, whereas prednisone was stopped. All blood parameters are normal, and the last echocardiogram showed normal cardiac kinesis (EF 61%), so we consider Still disease in remission.

3. Discussion

AOSD is considered an IL-1, IL-6, and IL-18-driven disease in which one of the major events in the pathogenesis is a dysregulation of inflammasome complex and a related overproduction of active IL-1b promoted by IL-18.[16]

In 1997, a phase III, randomized, double-blind, placebo-controlled, multicenter trial[17] evaluated the effectiveness of the addition of anakinra in the treatment of sepsis: 696 patients were randomized to anakinra 100 mg/d or placebo, followed by a 72-hour continuous intravenous infusion of either rhIL-1ra (2.0 mg/kg/h) or placebo. The trial was stopped early for not achieving the primary end point. It emerged that intravenous infusion of rhIL-1ra failed to demonstrate a statistically significant reduction in mortality when compared with standard therapy.

Shakoory et al[18] performed a subanalysis of Opal 1997 data, evaluating the effectiveness of treatment with anakinra versus placebo in patients showing laboratory tests indicative of MAS. Treatment with anakinra was associated with significant improvement in the 28-day survival rate in hepatobiliary dysfunction/disseminated intravascular coagulation patients (65.4% in anakinra vs 35.3% in placebo groups). Thus, they recognized a possible anakinra efficacy in the treatment of septic patients with MAS.

First-line treatment of AOSD has been classically based on nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, but only few cases fully respond to these common therapies.

The use of anakinra—receptor antagonist of IL-1—showed good results in refractory AOSD, as reported in different case reports and/or case series. In a multicenter study made of 22 patients with refractory AOSD in steroid therapy (prednisone >10 mg/d), anakinra led to remission more than NSAIDs therapies.[19]

In a multicenter open label trial, Ortiz-Sanjuán et al[5] recruited 41 patients with refractory AOSD and prescribed anakinra as monotherapy or in association with steroids or DMARDs. The improvement in clinical and lab manifestations was maintained during the follow-up, thus allowing a progressive reduction of the steroid dose and of the immunosuppression.

In our report, we described the case of a young patient with AOSD complicated by myocarditis and MAS despite to common therapies (steroid, cyclosporine) and the introduction of anakinra 100 mg/d in combination with conventional therapies. The patient had some negative prognostic factors for mortality in MAS according to 2 previous papers,[20,21] that is thrombocytopenia, elevated aspartate aminotransferase and increased serum ferritin levels. However, the main potentially fatal complication that the patient developed was fulminant myocarditis. It was therefore decided to increase the dose of the biologic drug up to

400 mg/d (8 mg/kg/d), with a gradual improvement. Although in Opa trial, the dosages achieved were almost 35 times higher than those indicated for the treatment of rheumatoid arthritis; to our knowledge, this is the first case in the literature in which supramaximal doses of anakinra were adopted for the treatment of myocarditis and MAS in AOSD. The initial dosages (1–2 mg/kg/d) can be insufficient and maximal dosages (up to 8 mg/kg/d) may be necessary in some AOSD as well as in Kawasaki or in cryopyrin-associated periodic syndrome patients.[22]

4. Conclusion

This is the first case report in which 8 mg/kg/d of anakinra have been used to treat a refractory AOSD complicated by MAS and myocarditis. Probably some patients need higher doses of Il-1 receptor blocker to switch off the hyper-inflammation as shown by Ombrello et al[23] in several cases of autoinflammatory syndromes.

References

[1] Bywaters EG. Still's disease in the adult. Ann Rheum Dis 1971;30:121–33.

[2] Pouchot J, Sampalis JS, Beaudet F, et al. Adult Still's disease: manifestations, disease course, and outcome in 62 patients. Medicine 1991;70:118–36.

[3] Moradinejad MH, Ziaee V. The incidence of macrophage activation syndrome in children with rheumatic disorders. Minerva Pediatr 2011;63:459–66.

[4] Schulert GS, Grom AA. Macrophage activation syndrome and cytokine-directed therapies. Best Pract Res Clin Rheumatol 2014;28:277–92.

[5] Ortiz-Sanjuán F, Blanco R, Riancho-Zarrabeitia L, et al. Efficacy of anakinra in refractory adult-onset Still's disease multicenter study of 41 patients and literature review. Medicine (Baltimore) 2015;94:e1554.

[6] Gerfaud-Valentin M, Sève P, Iwaz J, et al. Myocarditis in adult-onset Still disease. Medicine (Baltimore) 2014;93:280–9.

[7] Efthimiou P, Paik PK, Bielory L. Diagnosis and management of adult onset Still's disease. Ann Rheum Dis 2006;65:564–72.

[8] Espinosa G, Cervera R. Role of biologic therapy in systemic autoimmune diseases. Med Clin 2007;128:456–7.

[9] Vasques Godinho FM, Parreira Santos MJ, Canas da Silva J. Refractory adult onset Still's disease successfully treated with Anakinra. Ann Rheum Dis 2005;64:647–8.

[10] Kötter I, Wacker A, Koch S, et al. Anakinra in patients with treatment-resistant adult-onset Still's disease: four case reports with serial cytokine measurements and a review of the literature. Semin Arthritis Rheum 2007;37:189–97.

[11] Ortiz-Sanjuán F, Blanco R, Calvo-Rio V, et al. Efficacy of tocilizumab in conventional treatment-refractory adult-onset Still's disease: multicenter retrospective open-label study of thirty-four patients. Arthritis Rheumatol 2014;66:1659–65.

[12] Mahmud T, Hugher GR. Intravenous immunoglobulin in the treatment of refractory adult Still's disease. J Rheumatol 1999;26:2067–8.

[13] Yamaguchi M, Ohta A, Tsunematsu T, et al. Preliminary criteria for classification of adult Still's disease. J Rheumatol 1992;19:424–30.

[14] Pouchot J, Sampalis JS, Beaudet F, et al. Adult Still's disease: manifestations, disease course, and out come in 62 patients. Medicine (Baltimore) 1991;70:118–36.

[15] Fardet L, Galicier L, Lambotte O, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol 2014;66:2613–20.

[16] Giampietro C, Fautrel B. Anti-interleukin-1 agents in adult onset Still's disease. Int J Inflam 2012;2012:317820.

[17] Opal SM, Fisher CJJr, Dhainaut JF, et al. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial. The Interleukin-1 Receptor Antagonist Sepsis Investigator Group. Crit Care Med 1997;25:1115–24.

[18] Shakoory B, Carcillo JA, Chatham WW, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase III trial. Crit Care Med 2016;44:275–81.

[19] Nordström D1, Knight A, Luukkainen R, et al. Beneficial effect of interleukin 1 inhibition with anakinra in adult-onset Still's disease. An open, randomized, multicenter study. J Rheumatol 2012;39:2008–11.

[20] Arca M, Fardet L, Galicier L, et al. Prognostic factors of early death in a cohort of 162 adult haemophagocytic syndrome: impact of triggering disease and early treatment with etoposide. Br J Haematol 2015;168:63–8.

[21] Ruscitti P, Cipriani P, Ciccia F, et al. Prognostic factors of macrophage activation syndrome, at the time of diagnosis, in adult patients affected by autoimmune disease: analysis of 41 cases collected in 2 rheumatologic centers. Autoimmun Rev 2017;16:16–21.

[22] Kullenberg T, Löfqvist M, Leinonen M, et al. Long-term safety profile of anakinra in patients with severe cryopyrin-associated periodic syndromes. Rheumatology 2016;55:1499–506.

[23] Ombrello AK, Karyl B, Hoffmann PM, et al. An escalating dose of anakinra in patients with autoinflammatory disease is a safe and reasonable therapeutic option. Arthritis Rheum 2013;65(10 Supplement): S509.