

Fever of Unknown Origin with Polyarthritits Eken Y

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Abstract

We describe a 14-year-old male child presented with since 5 days of fever, polyarthritits and Salmon colored rash. For almost a century, this disorder is first recognized by George Frederic Still.

Keywords: Systemic onset of JIA; Juvenile idiopathic arthritis; Salmon colored rash; Polyarthritits; Auto-immune; Remitting fever

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Introduction

This disease has been defined as systemic arthritis by the International League of Associations for Rheumatology (ILAR) classification of juvenile idiopathic arthritis (JIA), 2 systemic-onset juvenile rheumatoid arthritis (JRA) by the American College of Rheumatology Classification, or systemic-onset juvenile chronic arthritis by the European League against Rheumatism classification. Diagnosis of systemic arthritis by the ILAR criteria requires the presence of arthritis and a documented quotidian fever of at least 2 weeks' duration, plus one of the following: typical rash, generalized lymphadenopathy, enlargement of liver or spleen, or serositis. Criteria and exclusions are shown in **Figure 1** and **Table 1**.

Systemic juvenile idiopathic arthritis: International League of Associations for Rheumatology (ILAR) diagnostic criteria

Arthritis in any number of joints together with a fever of at least 2 weeks' duration that is documented to be daily (quotidian) for at least 3 days and is accompanied by one or more of the following:

- Evanescent rash
- Generalized lymphadenopathy
- Enlargement of liver or spleen
- Serositis

Exclusions:

- Psoriasis or a history of psoriasis in the patient or a first-degree relative
- Arthritis in an HLA B27-positive male beginning after the sixth birthday
- Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter syndrome, or acute anterior uveitis—or a history of one of these disorders in a first-degree relative
- The presence of IgM RF on at least two occasions at least 3 mo apart

HLA, human leukocyte antigen; IgM, immunoglobulin M.

Figure 1 Most common clinical features of systemic onset of JIA [2].

Case Presentation

The patient complained of pain in the throat since 5 days, skin rash and fever up to 39°C with since 3 days pain and swelling in the wrist and ankles. Physical examination showed a child with normal vital signs. He was alert, good oriented in time/space and person. He had diffuse spread over his whole body salmon colored erythematous rash since 5 days (disappeared during admission after 6 days). ENT examination revealed red throat, Lymph nodules not enlarged. The lungs were clear to auscultation. There was no evidence of hepato-splenomegaly. Left knee painful at extension, not warmer than right knee, no swelling and painful wrists with limited movement [1-10].

Laboratory tests (**Table 2**) showed striking elevation in indicators of inflammation. CRP reached a maximum value of 259 (in first week of admission), BSE 77. White cell count is elevated (Leukocytes total number) and with a predominance of polymorphonuclear leukocytes (neutrophils). Thrombocytes at admission 359, increased to naar 600. Liver- and kidney function normal. LDH increased from 677 to 1018. ANA was negative, ANCA was negative. Reuma factors negative. Urine sedimentation was negative. Serologic tests for infection were negative for: Brucella, Bartonella, Leptospirase. EBV, Mycoplasma, Parvovirus B-19. Adenovirus, Coxsackie, Measles, CMV, Borrelia burgdorferi, Serologic tests for a bacterial infection with *Streptococcus* showed an elevation in the antibody titer. Microbiological cultures remained negative. Fecal, blood, throat, urine cultures showed no recent infection. Fecal cultures on *Salmonella* and *Shigella*, *Campylobacter*, *Yersinia* species was negative (**Table 2**) [11-18]. Mantoux test for tuberculosis infection was negative. Radiological examination revealed no signs of malignancy.

Roentgen image of thorax showed heart normal size, lungs normal, lymph nodules. Echo of abdomen showed normal liver, kidney, spleen. Skeleton scintigraphy showed increased uptake at left foot and left wrist; meaning poly-arthritis/poly-synovitis. Roentgen image of left knee showed osteochondritis dissecans. ECG was normal, no sign of pericarditis (no low voltage, no ST-segment elevation, no T-wave inversion) (Figure 2).

Discussion and Conclusion

This case study described a 14-year-old child with persistent fever since two weeks, rash, and polyarthritis. The onset of the disease with features of recurrent fever and polyarthritis is nonspecific and may suggest bacterial or viral infection, malignancy, or another inflammatory disease. The most common clinical features in 136 children with systemic-onset JRA were fever (98%), arthritis (88%) and rash (81%). Only 39% had lymphadenopathy, 10% had pericarditis, and fewer had hepato-splenomegaly [15]. Patient in our case had the required criteria for the diagnosis of systemic arthritis by the ILAR criteria. (Fever of at least 2 weeks duration plus typical rash). Criteria and exclusions are shown in **Tables 2 and 3** [2-8,19-27]. The clinical features are similar to Adult onset Still's disease [28-33]. When we compare our case of systemic onset JIA with Adult onset Still's disease criteria, then we come to conclusion that the required criteria for Diagnosis of Still disease is similar. Child described in our case has 5 major criteria (fever >39 longer than 1 week, arthritis, salmon colored rash, leukocytosis >10,000, with >80% neutrophils) and one minor criteria (negative Rheumatoid Factor and ANA) according to Yamaguchi. Our case had 3 major criteria and one minor criterion according to Fautrel. See for ILAR criteria (**Table 1**) and for criteria of Yamaguchi and Fautrel (**Table 2**) [2-8]. The possibility of a childhood vasculitis or malignancy is excluded by radiological investigations and other clinical investigations. These exclusion criteria are also named in ILAR criteria and criteria for Still's disease.

This case shows that not the presence of the clinical evident features in the onset but the evolution of the disease eventually made the diagnosis of systemic onset juvenile idiopathic arthritis. About 40% of the children with systemic JIA follow a monocyclic

Table 1 Criteria for Still's disease - Diagnostic criteria for adult onset Still's disease (AOSD), Yamaguchi's criteria [5-7].

Major criteria	Minor criteria
Fever >39°C, lasting 1 week or longer	Sore throat
Arthralgia or arthritis, lasting 2 weeks or longer	Recent development of significant lymphadenopathy
Typical rash	Hepatomegaly or splenomegaly
Leukocytosis >10,000/mm ³ with >80% polymorphonuclear cells	Abnormal liver function tests
--	Negative tests for antinuclear antibody (IF) and rheumatoid factor (IgM)

Other exclusion criteria are:

- Infections.
- Malignancies (mainly malignant lymphoma).
- Other rheumatic disease (mainly systemic vasculitides).

Five or more criteria are required, of whom two or more must be major.

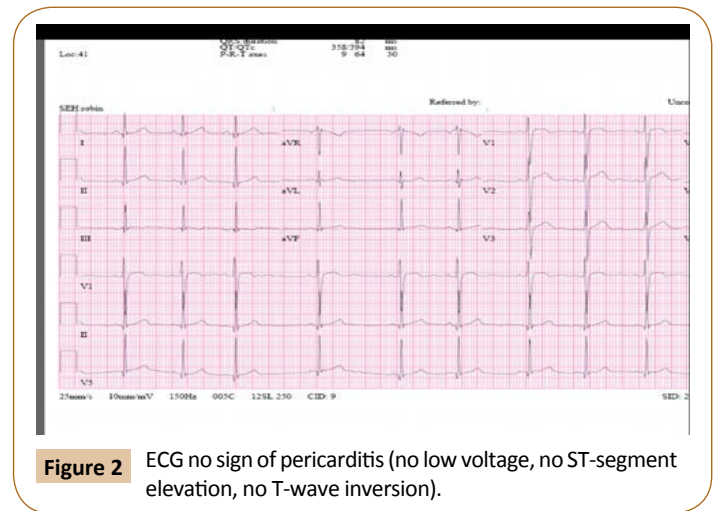


Table 2 Fautrel's criteria four or more major criteria are required or 3 major and 2 minor criteria [7].

Major criteria	Minor criteria
Spiking fever ≥ 39°C	Maculopapular rash
Arthralgia	Leukocytosis ≥ 10,000/mm ³
Transient erythema	--
Pharyngitis	--
Polymorphonuclear cells ≥ 80%	--
Glycosylated ferritin ≤ 20%	--

Note: Several diagnostic criteria have been proposed, Yamaguchi's and Fautrel's criteria being the most employed. For a discussion about the different criteria, see Mahroum N. et al., J. Autoimmunity 48-49: 34-37, 2014.

Table 3 Laboratory investigations.

Test	admission	Week 1	Week 2	Week3
Leucocytes	17.5	29.2	21	17.2
Neutrophils	15.1	25.4	18.6	13.2
CRP	164	259	217	45
BSE (mm/h)	--	77	63	45
LD	--	--	677	1018
Thrombocyt	359	521	441	--

Note: Day 1: Antistreptolysine O titer, AST (aggl) 437, Anti DNase B titer (aggl) 180.

disease course and eventually recover almost completely, after a variable period. A small proportion of children have a polycyclic course characterized by recurrent episodes of active disease interrupted by periods of remission without medications. Studies have shown that more than one-half of the children with systemic JIA have a persistent disease course which has resulted in progressive involvement of more and more joints and moderate to severe functional disability [16].

The most important early predictors of destructive arthritis are polyarthritis, thrombocytosis, persistent fever, or the need for systemic corticosteroids in the first 6 months after disease onset [17,18,34-39].

Treatment consisted in this case of NSAIDs. Patient received high dose Naproxen. Because of side effect is NSAID switched to

Indometacine retard 75 mg. With NSAID is used both to aid in control of the systemic inflammatory features (e.g., fever) and to modulate joint pain and inflammation. Because systemic features seldom respond satisfactorily to NSAIDs alone, if the diagnosis is firmly established, the early use of glucocorticoids is indicated. Intravenous methylprednisolone (30 mg/kg/day to a maximum of 1 g/day on 1 to 3 consecutive days) is effective in controlling systemic and articular features of the disease, but the effect is often short-lived. Therefore, oral prednisone (1 to 2 mg/kg/day to a maximum of 60 mg/day in one or more doses) is often necessary. Disease-modifying anti-rheumatic drugs have been traditionally used in patients with s-JIA, with the goal of sparing glucocorticoids, but their efficacy is usually limited. Although most of the evidence is provided by uncontrolled studies, biologic agents that inhibit the three pivotal inflammatory cytokines (TNF, IL-1 and IL-6) have already changed the approach to the treatment of s-JIA [40-45]. The role of especially IL-1 in the pathogenesis of s-JIA and predictors of response to IL-1 inhibition has been studied [22-25,44].

Abnormal expression of three of the most important pro-inflammatory cytokines-interleukin-6 (IL-6), IL-1, and tumor necrosis factor- α (TNF- α) is characteristic of systemic JIA. De Benedetti and Martini [33] suggested that systemic JIA is an IL-6-mediated disease. Evidence to support that hypothesis is strong. IL-6 is markedly elevated in the blood and synovial fluid. [34-36] The IL-6 level increases just before each fever spike and

correlates with the systemic activity of the disease, arthritis, and increase in acute phase reactants [37-41]. The abnormalities in regulation of IL-6 are also probably responsible for the limitation of growth, thrombocytosis and microcytic anemia seen in this disease [39,40].

There is accumulating evidence that inhibition of IL-1 or IL-6 is highly efficacious in a significant number of patients with persistent s-JIA, with improvements seen in both systemic symptoms and arthritis [19-21,26,28]. The long-term benefits of these approaches still need to be determined. One of the complications of systemic onset juvenile arthritis is macrophage activation syndrome (MAS). MAS bears close resemblance to secondary hemophagocytic lympho-histiocytosis (HLH) and is associated with serious morbidity and sometimes Death [29,30,46-49]. Other complication of systemic onset JIA is secondary amyloidosis. The outcome of JIA-associated amyloidosis in the Finnish series was also poor, with a mortality rate of 42% and renal insufficiency or renal transplantation required in 25% of survivors, after a mean follow-up of 15 years [32]. Autologous stem cell transplantation for systemic onset JIA can be a future remedy. There have been studies in the past [46-50].

Final Diagnosis

Systemic onset juvenile idiopathic arthritis.

References

- 1 Still GF (1897) On a form of chronic joint disease in children. *Med Chir Trans* 80: 47-59.
- 2 Petty RE, Southwood TR, Manners P (2004) International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J. Rheumatol.* 31: 390-392.
- 3 Evensen KJ, Nossent HC (2006) Epidemiology and outcome of adult onset Still's disease in Northern Norway. *Scand J Rheumatol* 35: 48-51.
- 4 Riera E, Olive A, Narvaez J (2011) Adult onset Still's disease: review of 41 cases. *Clin Exp Rheumatol* 29: 331-336.
- 5 Cush JJ, Medsger TA Jr, Christy WC (1987) Adult-onset Still's disease: clinical course and outcome. *Arthritis Rheum* 30: 186-194.
- 6 Yamaguchi M1, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, et al. (1992) Preliminary criteria for classification of adult Still's disease. *J Rheumatol* (1992) 19: 424-430.
- 7 Fautrel B, Zing E, Golmard JL (2002) Proposal for a new set of classification criteria for adult-onset Still disease. *Medicine (Baltimore)* 81: 194-200.
- 8 Baxevanos G, Tzimas T, Pappas G, Akritidis N (2012) A series of 22 patients with adult onset Still's disease presenting with fever of unknown origin. A difficult diagnosis *Clin Rheum* 31: 49-53.
- 9 Ogilvie EM, Fife MS, Thompson SD (2003) The -174G allele of the interleukin-6 gene confers susceptibility to systemic arthritis in children: a multicenter study using simplex and multiplex juvenile idiopathic arthritis families, *Arthritis Rheum.* 48: 3202-3206.
- 10 De Benedetti F, Meazza C, Vivarelli M (2003) Functional and prognostic relevance of the -173 polymorphism of the macrophage migration inhibitory factor gene in systemic-onset juvenile idiopathic arthritis, *Arthritis Rheum.* 48: 1398-1407.
- 11 Barnes MG, Grom AA, Thompson SD (2009) Subtype-specific peripheral blood gene expression profiles in recent-onset juvenile idiopathic arthritis. *Arthritis Rheum.* 60: 2102-2112.
- 12 De Jager W, Hoppenreijs EP, Wulffraat NM (2007) Blood and synovial fluid cytokine signatures in patients with juvenile idiopathic arthritis: a cross-sectional study, *Ann. Rheum. Dis.* 66: 589-598.
- 13 Frosch M, Ahlmann M, Vogl T (2009) The myeloid-related proteins 8 and 14 complex, a novel ligand of toll-like receptor 4, and interleukin-1 β form a positive feedback mechanism in systemic-onset juvenile idiopathic arthritis. *Arthritis. Rheum.* 60: 883-891.
- 14 Gattorno M, Piccini A, Lasiglie D (2008) The pattern of response to anti-interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis, *Arthritis Rheum.* 58: 1505-1515.
- 15 Behrens EM, Beukelman T, Gallo L (2008) Evaluation of the presentation of systemic onset juvenile rheumatoid arthritis: data from the Pennsylvania Systemic Onset Juvenile Arthritis Registry (PASOJAR), *J. Rheumatol.* 35: 343-348.
- 16 Spiegel LR, Schneider R, Lang BA (2000) Early predictors of poor functional outcome in systemic-onset juvenile rheumatoid arthritis: a multicenter cohort study, *Arthritis Rheum.* 43: 2402-2409.
- 17 Modesto C, Woo P, Garcia-Consuegra J (2001) Systemic onset juvenile chronic arthritis, polyarticular pattern and hip involvement as markers for a bad prognosis, *Clin Exp Rheumatol* 22: 211-217.
- 18 Sandborg C, Holmes TH, Lee T (2006) Candidate early predictors for progression to joint damage in systemic juvenile idiopathic arthritis, *J. Rheumatol.* 33: 2322-2329.
- 19 Pascual V (2005) Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. *Journal of Experimental Medicine* 201(9): 1479-1486.
- 20 Lequerre T (2008) Interleukin-1 receptor antagonist (anakinra) treatment in patents with systemic onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France. *Ann Rheum Dis* 67(3): 302-308.
- 21 Pascual V, Allantaz F, Arce E, Punaro M, Banchereau J, et al. (2005) Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. *J Exp Med* 201: 1479-1486.
- 22 Hashkes PJ, Uziel Y, Laxer RM (2010) The safety profile of biologic therapies for juvenile idiopathic arthritis. *Nat Rev Rheumatol* 6: 561-571.
- 23 Quartier P, Allantaz F, Cimaz R (2011) A multi centre, randomized, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic onset juvenile idiopathic arthritis (anajistrial). *Ann rheum dis* 70: 747-754.
- 24 Gattorno M, Piccini A, Lasiglie D (2008) The pattern of response to anti-interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis. *Arthritis Rheum* 58: 1505-1515.
- 25 Nigrovic PA, Mannion M, Prince FH (2011) Anakinra as first line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series. *Arthritis Rheum* 63: 545-555.
- 26 Puechal X, DeBandt M, Berthelot JM (2011) Tocilizumab in refractory adult Still's disease. *Arthritis Care Res* 63: 155-9
- 27 Franchini S, Dagna L, Salvo F (2010) Adult onset Still's disease: clinical presentation in a large cohort of Italian patients. *Clin Exp Rheumatol* 28: 41-48.
- 28 Yokota S, Imagawa T, Mori M (2008) Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomized, double-blind, placebo-controlled, withdrawal phase III trial, *Lancet* 371: 998-1006.
- 29 Sawhney S, Woo P, Murray KJ (2001) Macrophage activation syndrome: a potentially fatal complication of rheumatic disorders, *Arch. Dis. Child* 85: 421-426.
- 30 Stephan JL, Kone-Paut I, Galambun C (2001) Reactive haemophagocytic syndrome in children with inflammatory disorders: a retrospective study of 24 patients, *Rheumatology (Oxford)* 40: 1285-1292.
- 31 Ravelli M, Magni-Manzoni S, Pistorio A (2005) Preliminary diagnostic guidelines for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis, *J. Pediatr.* 146: 598-604.
- 32 Immonen K, Savolainen A, Kautiainen H (2008) Longterm outcome of amyloidosis associated with juvenile idiopathic arthritis, *J. Rheumatol.* 35: 907-912
- 33 De Benedetti F, Martini A (1998) Is systemic juvenile rheumatoid arthritis an inter-leukin 6 mediated disease? *J Rheumatol* 25: 203-207.
- 34 De Benedetti F, Massa M, Robbioni P (1991) Correlation of serum interleukin-6 levels with joint involvement and thrombocytosis in systemic juvenile rheumatoid arthritis. *Arthritis Rheum* 34: 1158-1163.

- 35 Lepore L, Pennesi M, Saletta S (1994) Study of IL-2, 1L-6, TNF alpha, IFN garruna and beta in the serum and synoviai fluid of patients with juvenile chronic arthritis. *Clin Exp Rheumatol* 12: 561-565.
- 36 Rooney M, David J, Symons J (1995) Inflammatory cytokine responses in juvenile chronic arthritis. *Br j Rheumatol* 34: 454-460.
- 37 Prieur AM, Kaufmann MT, Griscelli C (1987) Specific interleukin-I inhibitor in serum and urine of children with systemic juvenile chronic arthritis. *Lancet* 2: 1240-1242.
- 38 Mangge H, Kenzian H, Gallistl S (1995) Serum cytokines in juvenile rheumatoid arthritis: correlation with conventional inflammation parameters and clinical subtypes. *Arthritis Rheum* 38: 211-220.
- 39 De Benedetti F, Alonzi T, Moretta A (1997) Interleukin 6 causes growth impairment in transgenic mice through a decrease in insulin-like growth factor-I: a model for stunted growth in children with chronic inflammation. *Clin Invest* 99: 643-650.
- 40 Fishman O, Faulds G, Jeffery R (1998) The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. *Clin Invest* 102: 1369-1376.
- 41 De-Benedeni F, Massa M, Pignani P (1994) Serum soluble interleukin 6 (IL-6) receptor and IL-6/soluble IL-6 receptor complex in systemic juvenile rheumatoid arthritis. *Clin Invest* 93: 2114-2119.
- 42 Pignatti P, Ciapponi L, Galle P (2003) High circulating levels of biologically inactive IL-6/SIL-6 receptor complexes in systemic juvenile idiopathic arthritis: evidence for serum factors interfering with the binding to gp130. *Clin Exp Immunol* 131: 355-363.
- 43 De Benedetti F, Ravelli A, Martini A (1997) Cytokines in juvenile rheumatoid arthritis. *Curr Opin Rheumatol* 9: 428-433.
- 44 Pignatti P, Vivarelli M, Meazza P (2001) Abnormal regulation of interleukin 6 in systemic juvenile idiopathic arthritis. *Rheumatol* 28: 1670-1676.
- 45 De Benedetti F, Pignani P, Massa M (1995) Circulating levels of interleukin 1 beta and of interleukin 1 receptor antagonist in systemic juvenile chronic arthritis. *Clin Exp Rheumatol* 13: 779-784.
- 46 Keul R, Heinrich PC, Muller-Newen G (1998) A possible role for soluble IL-6 receptor in the pathogenesis of systemic onset juvenile chronic arthritis. *Cytokine* 10: 729-734.
- 47 Wulffraat NM, Brinkman O, Ferster A (2003) Long-term follow-up of autologous stem cell transplantation for refractory juvenile idiopathic arthritis, *Bone Marrow Transplantation* 342: 561-564.
- 48 Quartier P, Prieur AM, Fischer A (1999) Haemopoietic stem-cell transplantation for juvenile chronic althritis. *Lancet* 353: 1885-1886.
- 49 Prieur AM, Stephan IL (1994) Macrophage activation syndrome in rheumatic dis-eases in children. *Rev Rhum Ed Fr* 61: 447-451.
- 50 Sawhney S, Woo P, Murray K (2001) Macrophage activation syndrome: a potentially fatal complication of rheumatic disorders. *Arch Dis Child* 85: 421-426.