

## Research Article

# The Challenges in the Diagnosis and Treatment of Still's Disease

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## Abstract

Adult onset Still's disease (AOSD) is a rare disease in adults, in children also known as systemic juvenile idiopathic arthritis. We describe two patients with intermittent fevers without unknown origin. 27 years man and 75 years old woman, who presented with lymphadenopathy and recurrent fevers, There has been used intensive serologic, radiologic, laboratory investigation to exclude infectious diseases and malignancy. All the investigation showed no diagnosis. The clinical disease described for the first time at 1897 by Dr Still is finally diagnosed. Both patients received Anakinra with rapid response in hematologic, biochemical, and cytokine markers with reduction of systemic and local inflammation.

**Keywords:** Systemic JIA; Juvenile Idiopathic Arthritis; Remitting Fever; Autoimmune; Macular or Maculopapular Exanthema; Low-Grade Persistent Fevers; Biological; IL-1B Antagonist, Still's Disease

## Introduction

### Adult-onset still's disease (AOSD)

AOSD is a rare systemic inflammatory disease of unknown etiologic that often presents as a fever of unknown origin. Systemic features, such as spiking fever, skin rash, generalized lymphadenopathy, hepatomegaly, splenomegaly, and serositis, was first described by the British paediatrician George F. Still in 1896 [1] and by Bywaters in 14 patients in 1970 [2]. The aetiology of AOSD still remains unknown, but over expression of Th1 cytokines and IL-1 may have a critical role [3]. Pericarditis, pleural effusions, and severe abdominal pain may be present and confound diagnosis [4].

Daily fevers, evanescent rash, arthritis, hyperferritinemia, and liver dysfunction were consistent with AOSD [5-7]. Hyperferritinemia has a high sensitivity for AOSD (80%) but has a low specificity (40%) [8]. the fraction of glycosylated ferritin is higher than with inflammatory conditions. The combination of elevated serum ferritin level and low (20%) fraction of glycosylated ferritin can make the diagnosis of AOSD most likely [6]. In fact AOSD has similarities to auto inflammatory diseases, as exemplified by a central role of the innate immune system and by the cytokines involved (e.g., interleukin-1B [IL-1B]) [10,11]. Moreover, the blocking of both IL-1B has been shown to be efficacious in the treatment of AOSD [12,13]. Anakinra, IL-1B receptor antagonist, has been studied in AOSD, with favorable results [14,15]. AOSD patients had significant improvement with anakinra. In a study by Pascual and coworkers, seven of nine patients with AOSD had an excellent response to IL-1B inhibition [16].

## Case Reports

### Case 1

A 27-year-old Caucasian male presented at his first admission with an episode of fever since 4 weeks, diffuse myalgia, soar throat, cold chills and fatigue. The patient was in his usual state of health until 1 month before admission, when he developed fever. He had an 18-pound weight loss over the preceding month. During the fever attacks he had fatigue. The patient's medical history was unremarkable except an episode of fever after a streptococcal infection ten years ago. There was no family history of autoimmune diseases. He was on low dose Diclofenac as medication upon admission.

Physical examination showed normal vital signs with fever of 40.0° Celsius (104° F). The remainder of the physical examination was unremarkable.

Laboratory test revealed elevated inflammatory markers, including erythrocyte sedimentation rate (ESR; 116 mm/hour), C-reactive protein level (266mg/litter). A peripheral leucocytosis was present, with a white blood cell count of 22 000/mm<sup>3</sup> (normal range 4,500–11,000). WBCs, 90 % neutrophils. The serum ferritin level was markedly increased at 5696 ng/ml (normal range 10–200). Urine cultures showed no infection and proteinuria was absent. An infectious disease evaluation was performed and was negative. Serologic study of Rheumatoid factor and anti nuclear antibody was negative. Antibodies to Sm/RNP, Ro/SSA, and La/SSB; anti cardiolipin antibodies; ant neutrophil cytoplasmic antibodies (ANCA); and anti-cyclic citrullinated peptide antibodies were negative, and creatinine phosphokinase was normal. A chest radiograph was normal. Transoesophageal echocardiogram was performed by cardiologist the next day and ruled out endocarditic. (No vegetation's, some pericardial fluid).

After being well during 1 year after hospital discharge he complained

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of since 1 month existing fatigue, diarrhoea, nausea, vomiting, with fever up to 40.3° Celsius (104.54° F). He had recognized dark urine and light coloured defecations. Physical examination at his second admission showed a sick patient with dry mucosa. Blood pressure 123/55, icteric skin, decreased skin turgor. Submandibular, right lateral sternocleidomastoid and right groin lymphadenopathy, all noduli seemed benign. Temperature was 38.9° degrees Celsius (102° F), the pulse rate was 122 beats/ minute, and the respiratory rate was 12 breaths/minute. Abdomen is extended with normal with normal bowel sounds, splenomegaly and hepatomegaly 10 cm below the costal arch. His liver function deteriorated and clotting indices were also deranged.

Liver biopsy showed no specific inflammation. See Image 1. Prednisone 60 mg/day was started. The patient's localized rash and fever resolved spontaneously. Liver function showed improvement. He was discharged from our hospital after 3 weeks.

## Case 2

75 years old women presented at our hospital with since months daily fevers between 38 to 39.5° Celsius (100.4°-103.1° F) with night sweats. Her complaints were of fatigue, dizziness and nausea. Besides the febrile episode she felt well. Attacks of fever occurred sometimes 2 times a day and reached normal level. She lost 10 kilograms in 1 month. There was no family history of autoimmune disease. She had Diabetes Mellitus type II, atrium fibrillation in medical history and used atenolol/chlortalidon 1dd100/25 mg, Metformin 2dd500 mg.

Physical examination revealed fully alert, oriented, and lucid sick women. Her vitals sign were as follows. Blood pressure 150/80 mm Hg, Heart beat 76/minute, her oxygen saturation was 95% on

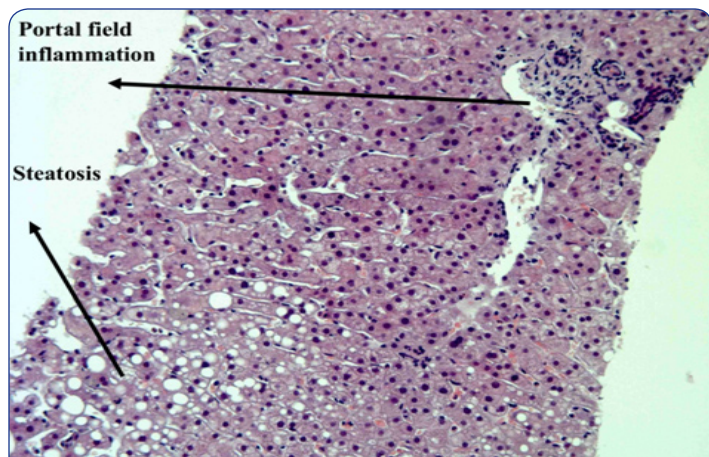


**Figure 1.** Liver biopsy of Case 1 (Hematoxylin-eosin stain, original magnification 400x)

Pathology report: Chronic non specific hepatitis , no necrosis and only slight inflammation at portal field . The biopsy of the liver and lymph nodule biopsy showed no typical sign of malignancy, tuberculosis infection, other infectious cause, sarcoidosis or Kikuchi disease. The only finding at histological examination was nonspecific reactive para cortical hyperplasia.

room air, and Temperature 37.8° Celsius (100° F), her respiratory rate was 18 breaths/minute unlaboured. Unilateral right sided supraclavicular lymphadenopathy with right thyroid gland nodule. Examination of her heart revealed an irregular tachycardia (atrial flutter on ECG) but no murmurs, rubs, or gallops. The lungs were clear to auscultation. There was no evidence of hepatosplenomegaly, skin rash, focal motor weakness, sensory deficits or arthritis. Laboratory examination showed elevated inflammation levels (CRP 133 mg/L, BSE 48 mm/h). Leucocytes 13.1/nL Neutrophils 11/nL , Calcitonin lightly elevated. No M protein detectable, ACE not elevated. Assays for antinuclear antibodies, antibodies to double stranded DNA, rheumatoid factor, anti-neutrophil cytoplasmic antibodies, anti-phospholipid antibodies, and cryoglobulins were negative. The serum C3 and C4 levels were normal. A serum protein electrophoresis test showed normal levels of all immunoglobulin and no monoclonal spike. Blood cultures and a tuberculin test were negative. ECG: Atrium flutter. A complete work-up, including lymph node, bone marrow biopsy, was done to exclude malignancy. Her blood, stool, urine cultures and viral serology were all negative. All serologic examination was negative. Chest radiogram showed cardiomegaly. An ultrasound scan of the abdomen showed no abnormalities. CT thorax showed multiple pathologic mediastinal lymphomas (Figure 2).

Pet scan revealed elevated uptake of contrast (iodinated intravenous barium) in multiple pathologic nodules, high supraclavicular right and mediastinal (Figure 3). Mediastinal lymph nodule biopsy showed no malignant cells, only non-specific reactive Para cortical hyperplasia. Cytological puncture thyroid gland nodule was normal. Bronchoscopy revealed normal lower airways.

During Hospital admission of 7 weeks, she had daily fever attacks with hypotension during febrile episode and 2 periods of 4-5 days without fever. Most of the febrile attacks occurred at night or early

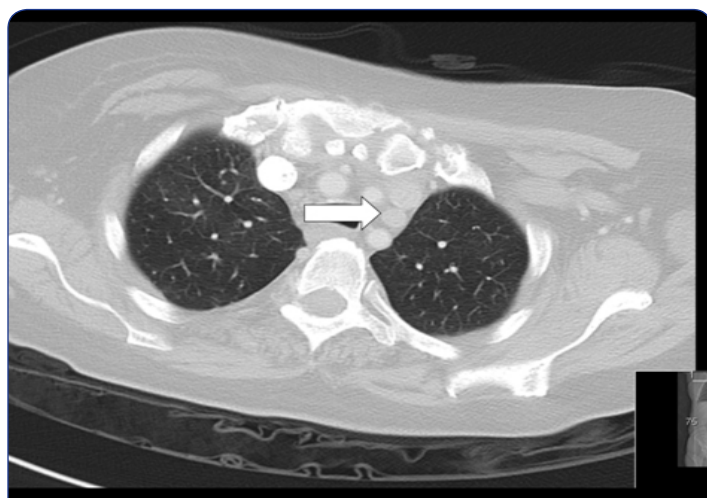


**Figure 2:** Figure 2 Patient B Ct thorax: multiple lymph nodules increased in size

Gantry 0 degrees, FoV: 312 mm, Time 500 ms, Slice 5 mm, 486 mA, 120 kV 14th slice from 75

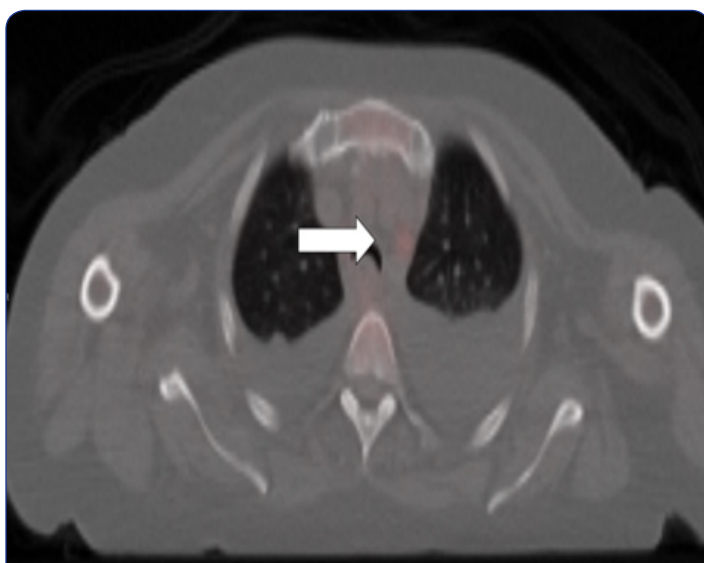


**Figure 3:** Pet Scan Thorax

Pet scan revealed elevated uptake of contrast (iodinated intravenous barium) in multiple pathologic nodules (mediastinal nodules visible)

in the morning. At the beginning of the hospital stay were the levels of fever higher than compared with the last weeks. She developed during 2nd week pericarditis. Except for the fever attacks she was hemodynamic stable; only during a febrile attack she had hypotension and fatigue. She received Anakinra with clinical remission. There was an initial response without relapse.

### General Discussion

Diagnosis of AOSD can be challenging, due to the reason that there is no specific test available for the diagnosis. AOSD is often confounded with infections, malignancies, other autoimmune disorders as necrotizing vasculitis, hypersensitivity drug reactions. The typical features of AOSD are high spiking fever, evanescent rash, and arthritis or arthralgia. Not all these symptoms need to be present at onset sometimes they occur after months; like in case 1 the rash is not present at onset. The pleiotropic manifestations range from no lymph nodules to sudden onset of rash after years. Atypical manifestations of AOSD cause a delay in diagnosis and treatment like in case 2.

Several criteria sets are available for accurate diagnosis of AOSD. Diagnostic criteria for AOSD are described by Yamaguchi and Fautrel (table 1). Yamaguchi criteria have a long list of diseases that must be excluded (for example malignancies of the lymph reticular system). The Fautrel criteria which are more specific require the not ready available measurement of glycosylated ferritin.

Case 1 met the 5 acquired criteria from which 2 major criteria for the Diagnosis of adult onset Still's disease according to Yamaguchi et al 1992 see table 3. In Case 1 presented with 3 major criteria (spiking fever, pharyngitis, glycosylated ferritin < 20 %) and 3 minor criteria (maculopapular exanthema, leukocytosis of 22,000 / mm<sup>3</sup> WBC 90 % neutrophils, abnormal liver enzyme tests). Case

2 had two major criteria according to Yamaguchi et al (spiking fever > 39 °C, had Leucocytosis 13 100 with 84 % consisting from neutrophils). Case 2 had 2 minor criteria namely negative serologic tests for anti nuclear antibody and rheumatoid factor, recently developed Lymphadenopathy. Case 2 had a few nodules supra-clavicular. After radiological investigation there were multiple mediastinal nodules in Case 2. Malignancy especially Lymphoma and leukaemia are excluded by biopsy. High fever, rash, liver dysfunction, ferritin can be consistent with sepsis. Endocarditis should also be considered. Both patients thought to have an infection as a most probable cause of fever. Serologic examination revealed no infectious cause. In both patients Cardiologist excluded an endocarditic. Case 2 had the 4 acquired major criteria according Fautrel see table 3. Spiking fever longer than 2 weeks, Polymorphonuclear cells > 80%, elevated ferritin from which glycosylated ferritin < 20 % and erythema. Case 2 had one minor criteria according to Fautrel namely leucocytosis. Both cases met the acquired criteria for diagnosis of AOSD. Yamaguchi criteria have been used for diagnosis of AOSD in case 1. Fautrel criteria for case 2. Immune response dysregulation is thought to be reason of inflammation in AOSD. Pro inflammatory cytokines are elevated especially IL-1β. IL-1β (also termed IL-1) is prototypic proinflammatory cytokines that activate effectors cells by binding to IL-1 receptors [28]. The production of mature and bioactive IL-1β is regulated by two signals: signal 1 induces the production of pro-IL-1β.

Activation of the inflammasome, a cytosolic complex of proteins, leads to the activation of caspase-1, which causes processing of pro-IL-1β into mature IL-1β and its release outside the cells.

In addition to caspase-1, other enzymes are also involved in the cleavage and maturation of IL-1β [30]. Exogenous microbial components and endogenous agents (monosodium urate and calcium dihydrate pyrophosphate crystals) can activate the NALP3 inflammasome.

In addition, some mutations of NALP3 lead to spontaneous activation of the inflammasome and caspase-1 and overproduction of IL-1β, which causes recurrent episodes of fever with inflammatory systemic manifestations [29,32,33,35].

Use of IL-1 inhibitors has been particularly successful in conditions associated with acute inflammatory flares, the presence of neutrophilic infiltrates, and also sometimes blood neutrophilia. Unfortunately, because blood levels of IL-1 are only marginally elevated or most often undetectable, they are of no value in predicting response to IL-1 inhibitors. In healthy human subjects, IL-1β, contrary to other cytokines, is barely detectable in the bloodstream, thus suggesting that its circulating levels are below 10 pg/mL. Such low levels have to be maintained because of the tremendous potency of IL-1β in inducing inflammatory responses [30]. Experimental evidence indicates that IL-1 is involved in the development of arthritis [31].

|                        | Cush et al (1987) <sup>5</sup>                                                                                             | Yamaguchi et al (1992) <sup>6</sup>                                                                                                                                                                                                                                                                                                                       | Fautrel et al (2002) <sup>7</sup>                                                                                                                                                                                                  |
|------------------------|----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Design                 | Single center, retrospective                                                                                               | Multicenter, retrospective                                                                                                                                                                                                                                                                                                                                | Single center, retrospective                                                                                                                                                                                                       |
| Data analysis          | Descriptive                                                                                                                | Discriminatory statistical analysis                                                                                                                                                                                                                                                                                                                       | Logistic regression analysis                                                                                                                                                                                                       |
| Cohort size            | 21                                                                                                                         | 90                                                                                                                                                                                                                                                                                                                                                        | 72                                                                                                                                                                                                                                 |
| Disease duration       | 11.8 years                                                                                                                 | 3.8 years                                                                                                                                                                                                                                                                                                                                                 | 2.9 years                                                                                                                                                                                                                          |
| Case definition        | Fever $\geq 39^{\circ}\text{C}$ and arthralgia/arthritis with any 2 of: leukocytosis, JRA, rash, serositis/RES involvement | Clinical diagnosis upheld after case review by expert committee                                                                                                                                                                                                                                                                                           | Patients undergoing ferritin measurement and clinical diagnosis upheld after prolonged observation and case review by one expert                                                                                                   |
| Excluded from analysis | RF > 1:80<br>ANA > 1:100                                                                                                   | Non-definite cases after review (n = 56)                                                                                                                                                                                                                                                                                                                  | Non-definite cases after review                                                                                                                                                                                                    |
| Comparator group       | None                                                                                                                       | 267 definite non-AOSD cases                                                                                                                                                                                                                                                                                                                               | 130 definite non-AOSD cases                                                                                                                                                                                                        |
| Criteria set           | Fever $\geq 39^{\circ}\text{C}$ and arthralgia/arthritis with any 2 of: leukocytosis, JRA, rash, serositis/RES involvement | <i>Major:</i> Fever $\geq 39^{\circ}\text{C}$ for > 1 week, arthralgia > 2 weeks, maculopapular non-pruritic salmon-pink rash, leukocytosis $\geq 10,000/\text{mm}^3$ with $\geq 80\%$ neutrophils<br><i>Minor:</i> Pharyngitis or sore throat, lymphadenopathy, and/or splenomegaly, abnormal aminotransferases, negative rheumatoid factor or ANA assay | <i>Major:</i> Spiking fever $\geq 39^{\circ}\text{C}$ , arthralgia, transient erythema, pharyngitis, neutrophils > 80%, glycosylated ferritin fraction < 20%<br><i>Minor:</i> Typical rash, leukocytosis $\geq 10,000/\text{mm}^3$ |
| Required               | As above                                                                                                                   | At least 5 criteria, including 2 major                                                                                                                                                                                                                                                                                                                    | Four major criteria or 3 major and 2 minor criteria                                                                                                                                                                                |
| Exclusion needed       | None                                                                                                                       | Infections, malignancies, vasculitides                                                                                                                                                                                                                                                                                                                    | None                                                                                                                                                                                                                               |
| Sensitivity for set    | Not analyzed                                                                                                               | 96%                                                                                                                                                                                                                                                                                                                                                       | 81%                                                                                                                                                                                                                                |
| Specificity for set    | Not analyzed                                                                                                               | 92%                                                                                                                                                                                                                                                                                                                                                       | 98%                                                                                                                                                                                                                                |

JRA, juvenile rheumatoid arthritis; RES, reticuloendothelial system; RF, rheumatoid factor; ANA, antinuclear antibody.

#### Diagnostic criteria for AOSD

| References in table | Reference number | Name of criteria       |
|---------------------|------------------|------------------------|
|                     | 6                | Yamaguchi et al (1992) |
|                     | 7                | Fautrel et al (2002)   |

Note: criteria sets proposed to assist in distinguishing aosd patients

IL-1 inhibitors have been reported to be markedly effective in the management of systemic-onset juvenile idiopathic arthritis, adult-onset Still disease [11]. For the evidence that exists of the use of antagonists of IL-1B in the literature [12-16].

In case 1 the first 7 years after onset of AOSD corticosteroids and at fourth year from onset of AOSD is modifying anti rheumatoid drug (DMARD) Methotrexate (MTX) added with good response. Only after years and two severe relapses of AOSD by an unresponsive disease course treatment with DMARD MTX and corticosteroid is switched to biological IL-1B antagonist. Two months after start systemic inflammation and fever attacks improved. The liver function and inflammatory parameters are normalized.

Case 2 did not receive corticosteroids as first choice because of presence of dysregulated diabetes mellitus type II. The use of corticosteroids has an unavoidable side effect on blood glucose levels on patients with Diabetes Mellitus that is dysregulated due to AOSD episode.

She had a 2 months long admission with multiple investigations without proper treatment. To shorten her quality of life as soon as possible, at second month of admission is the treatment with IL-

1B antagonist started. Methotrexate is relatively slow acting drug (response starts weeks after first intake) compared with IL-1B antagonist. The response to IL-1B inhibitors is very rapid compared with MTX and occurs within days and sometimes a few hours after the initiation of therapy. In other patients especially children and young adults, the first choice of treatment remains corticosteroids and DMARDs [17,18,22].

The feasibility of IL-1B antagonist is limited by the fact that it is currently available only as a daily subcutaneous injection that causes significant burning and pain. This pain is caused by allergic reaction (mast cell degranulation) after administration of the vehicle constituents in combination with a relatively large amount of anakinra in a highly concentrated protein [23]. Another side effect or toxic effect of IL-1B antagonist is that it can cause neutropenia and serious infections if it is concurrent administered with biological Enbrel(TNF inhibitor). Patients who already have neutropenia should not start with IL 1B antagonists. Only 2 % of adult patients that started with IL-1B antagonist had a decrease in neutrophil count but no neutropenia.

In Children there are more adverse effects of IL-1B antagonists

reported. The major adverse effects of anti-IL-1 therapy include injection site reaction (anakinra; rilonacept; canakinumab) and infections, particularly gram-positive (especially pneumococcal) infections [24]. Up-to-date vaccinations, including pneumococcal vaccination, should be ensured in children receiving anti-IL-1 therapy.

Macrophage activation syndrome (MAS) could be the initial form of AOSD [36]. However appearance of this complication during diagnostic process or evolution of disease is most common. It is even possible to have an induction of MAS by children treated with IL-1B antagonists. Macrophage activation syndrome has severe consequences if left untreated (cytopenia, hypertriglyceridemia). Bone marrow aspiration and biopsy is needed for diagnosis of MAS. Treatment of MAS consists of pulse corticosteroids methylprednisolone intravenous, intravenous immune globulins, cyclosporine.

MAS can be a complication of treatment with anti IL1B antagonists in children. MAS can also a form of AOSD which needs to be treated with IL1B antagonists.

Autologous stem cell transplantation (ASCT) can be an option for treatment of AOSD and for children with systemic onset juvenile idiopathic arthritis (childhood form of AOSD). Still a big price for a therapy induced complication....

## Final Diagnosis

Adult Onset Still's Disease

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