CASE REPORT

Adult-Onset Still's Disease: Delayed Diagnosis Persists.

Wahinuddin Sulaiman, Farisya Mohd Lepatoni.

Faculty of Medicine, Universiti Kuala Lumpur Royal College of Medicine Perak, Ipoh, Perak, Malaysia.

Corresponding Author
Dr. Wahinuddin Sulaiman
Clinical Professor, Faculty of Medicine, Universiti Kuala Lumpur Royal College of Medicine Perak, No. 3, Jalan Greentown, 30450 Ipoh, Malaysia.
Email: wahinuddin@unikl.edu.my / nwahin@gmail.com

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Abstract

Adult-onset Still's disease (AOSD) is a rare inflammatory condition of unknown etiology, that is characterised by quotidian high spiking fever, polyarthritis, evanescent rash, and hyperferritinemia. AOSD is a diagnosis by exclusion, and it is one of the common causes of pyrexia of unknown origin (PUO) which can be life threatening if mistreated. Treatment may pose a great challenge. We report a young woman who presented with PUO, rashes, progressive and debilitating polyarthritis for 10 months duration. Serological markers were negative except for ANA (speckled pattern, 1:160). Serum ferritin, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were markedly raised. She achieved remission after about 6 months of treatment with a combination of multiple immunosuppressants and corticosteroids.

Keywords: *Adult-onset Still's disease, hyperferritinemia, pyrexia of unknown origin.*

Introduction

Adult-onset Still's disease (AOSD) is a rare auto-inflammatory disorder of unknown etiology, commonly affecting young adults. AOSD bears a resemblance to systemic juvenile idiopathic arthritis (SJIA), that was first described by George Still in 1897[1]. In 1970s, Eric Bywaters described AOSD as a distinct clinical entity. AOSD is classically characterized by spiking fever, arthritis, and salmon-coloured skin rash [2].

Globally, the incidence of AOSD is estimated to be between 0.16 and 0.62 per 100,000 individuals of various ethnicities, with an estimated prevalence of 0.73 to 6.77 per 100,000.. Japan and Turkey have reported higher prevalence rates (3.9 and 6.77 per 100,000, respectively) [3 -6].

It is diagnosed by exclusion since there is an unavailability of diagnostic tools. AOSD may have protean clinical manifestations which may be indistinguishable from other inflammatory joint diseases like rheumatoid arthritis. Patients commonly present with PUO as in these cases. If left untreated, AOSD may lead to fatal complications such as macrophage-activation syndrome (MAS) [7].

We present a young woman with unresolved high fever for 10 months that met the PUO criteria [8], as well as progressive and debilitating polyarthritis. The patient has fulfilled 4 major and one minor Yamaguchi's criteria for AOSD [9].

Case report

A 20-year-old lady, a pharmacy student, who had previously been well, was presented with a high spiking fever, progressive symmetrical polyarthritis, and morning stiffness lasting more than 4 hours that had been present for more than 10 months. She was initially treated for rheumatoid arthritis with methotrexate but developed allergic reactions before being referred to a rheumatologist. Her arthritis and fever were relieved temporarily with corticosteroid, but they recurred and left her debilitated. She was unable to ambulate and was wheelchair bound for over a month. She neither had any signs and symptoms suggestive of systemic lupus erythematosus (SLE) nor systemic involvement of other autoimmune disorders.

Physical examination revealed a non-toxic, pale-looking patient with a temperature of 39^{o}C. There was active synovitis of the wrists, proximal interphalangeal and metacarpophalangeal joints, elbows, and shoulders, as well as the knees, ankles, and tarsals. (Figure 1). Faint erythematous rashes were noted on the abdominal wall. Traube's space was dull, suggestive of splenomegaly but there was no hepatomegaly. Peripheral lymph nodes were not palpable. The rest of the systemic examination was unremarkable.

Laboratory investigation (Table 1) shows marked leukocytosis with neutrophilia and hypochromic microcytic anemia. Both the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and serum ferritin were markedly elevated. The serum fibrinogen was mildly raised. The cholesterol levels and the liver enzymes were within normal range. She underwent extensive work-up with a battery of tests including repeated septic workouts, imaging (chest radiograph, computed tomography and ultrasonography of the abdomen), hepatitis B and C screening, dengue, and Chikungunya serologies which all came out negative. The immunological markers were negative except for ANA. The computed tomography (CT) scan confirmed the clinical findings of splenomegaly.

Based on the presentation and the laboratory findings, she was diagnosed with Adult-Onset Still's Disease (AOSD) of which she fulfilled Yamaguchi's criteria for AOSD [9]. She was given intravenous (IV) methylprednisolone 500 mg daily for 3 days followed by a tapering dose of prednisolone, tramadol, and calcium

supplement. Since she was unsure of allergy to methotrexate (MTX), cyclosporin 75 mg twice daily and hydroxychloroquine 200 mg were prescribed instead. Her symptoms (polyarthritis, fever, and general wellbeing) improved over the next few days, and the acute phase reactants (ESR, CRP and serum ferritin) level normalised. During the next month of follow-up, prednisolone was tapered down to 7.5 mg daily. Despite the initiation of double immunosuppressants, she experienced a relapse that resolved after adding azathioprine 50 mg daily and salazopyrine 500 mg twice daily to her treatment regimen.

She was treated for latent tuberculosis as tuberculosis (TB) interferon-γ release assays (IGRAs) (QuantiFERON Gold test) repeatedly came out with indeterminate results, with a view of starting interleukin-6 (IL-6) inhibitor to optimize her treatment. However, IL-6 inhibitor treatment was declined due to cost factor. Nevertheless, with good compliance, she was asymptomatic and has achieved satisfactory remission without untoward effects from multiple combinations of immunosuppressants or resulting in physical disability. The quadruple immunosuppressants were discontinued after 10 months of treatment. She was then challenged with MTX 7.5 mg weekly and folate 5 mg weekly, with no allergic reaction, noted.

Discussion

Adult-onset Still's disease (AOSD) is a rare inflammatory joint disorder of obscured etiopathogenesis. The classical clinical manifestations of AOSD are recurring high grade fever, arthritis which may be severe and presence of evanescent rash [2]. The criteria and classification (Table 2) had been reviewed based on the advancement in scientific evidence in the pathogenesis of AOSD [9,10]. AOSD has been classified as polygenic autoinflammatory disorder based on the presence of inflammatory cytokines (, IL-1β, IL-18, IL-6, and anti-TNF) that were postulated to be involved in the pathogenesis of AOSD [11-13]. Nevertheless, the exact trigger has yet to be identified.

Petros et al. conducted a large systematic review that revealed heterogeneity and ambiguity in the clinical presentation of AOSD, which led to delays in diagnosis and treatment. The risk of a life-threatening complication with high mortality rate, such as macrophage activation syndrome (MAS), is substantially higher in some of the studies [14]. Another factor contributing to the late diagnosis of AOSD is a lack of diagnostic tools, such as specific biomarkers, despite the discovery of specific interleukin subtypes (IL-1, IL-18). These tests are not easily available in many countries due to financial constraints.

Working out for other causes of PUO is usually a routine practice and a daunting process before diagnosing AOSD particularly infections and malignancies. This also may hamper making the diagnosis of AOSD. To date, AOSD diagnosis is made by exclusion using Yamaguchi's criteria which has high sensitivity and specificity (96.1% and 91.2%, respectively) [9].

Apart from haematological criteria, hyperferritinemia has been reported as a common finding in AOSD despite being a poor predictor in the absence of clinical features. It has been shown that glycosylated ferritin has high specificity (93%) for AOSD when combined with total ferritin level greater than 5-folds of normal value [15]. This patient's serum ferritin level was indeed markedly raised together with other acute phase reactants.

Full blood analysis revealed microcytic hypochromic anaemia likely due to iron deficiency anaemia or thalassaemia [16 -20]. However, improvement in MCV and MCH after receiving treatment for AOSD favoured none of them. Unexpectedly, ANA test was positive but there were reporANA-positive cases [21-23]

This patient fulfilled Yamaguchi's criteria for AOSD. The erythematous rashes she developed and claimed were caused by methotrexate allergy is uncertain. It is likely to be the typical AOSD rash as it was transient, although it was pruritic in nature. When MTX was taken for the second time, no allergic reaction was noted. The worsening of her symptoms over a 10-month period, with frequent relapses, raises the possibility of life-threatening complications i.e., MAS. The diagnostic criteria of MAS in AOSD consist of serum ferritin > 684 ng/ml and two of the following- platelet counts < 181,000 per mm^3, aspartate aminotransferase > 48 U/L, triglycerides > 156 mg/dL, and fibrinogen < 3.6 g/L in accordance with the European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation (EULAR/ACR/PRINTO) criteria 2016 [24]. Although the fibrinogen was raised, other contributing risk parameters were absent, and she responded well to corticosteroid. However, due to her relapses, additional immunosuppressants were added, and her symptoms eventually resolved without any adverse events.

Treatment of AOSD is daunting with the possibility of life-threatening complications. There are no specific treatment guidelines or recommendations for AOSD due to its rarity. Corticosteroid and non-steroidal anti-inflammatory medications are the mainstay of treatment. Methotrexate, one of the steroid-sparing agents, has been reported to induce remission in 70% patients with AOSD [25]. Disease modifying anti-rheumatic drugs (DMARDs) including interleukin inhibitors [26, 27], TNFα and targeted synthetic DMARD (Janus-kinases inhibitors) usually used in refractory cases of AOSD to corticosteroids and conventional synthetic DMARDs [28, 29].
AOSD is classified into three distinct phenotypes i.e., self-limiting or monophasic, intermittent or polycyclic and chronic evolution based on the clinical course [30 - 32]. Figure 2 summarizes the treatment consensus for AOSD.

In this case, the patient initially claimed unable to tolerate methotrexate, so she was switched to cyclosporin and hydroxychloroquine. Other immunomodulators following relapse episode were added for the optimization of therapy. This combination enabled this patient to achieve a satisfactory remission period in which all her symptoms, including laboratory parameters, were resolved. AOSD, on the other hand, has an unpredictable course and can become refractory. It is recommended to use IL-1 inhibitor (anakinra) [33] or IL-6 inhibitor (tocilizumab) [34] for refractory cases of AOSD. However, the high cost implicated, as well as the indeterminate result of IGRA, have become the barriers to using these drugs in this patient.

Conclusion

AOSD is a rare autoinflammatory systemic disorder with obscured etiology and pathogenesis. It is a diagnosis by exclusion, and diagnosis is frequently delayed. The discovery of biomarkers for AOSD does not help to expedite the diagnosis algorithm. Nonetheless, clinicians ought to have a high index of suspicion when patients present with PUO without symptoms and signs of other causes of PUO, or prolonged fever. The current guideline based on Yamaguchi's criteria should aid in the early diagnosis of AOSD and treatment to avoid catastrophic and life-threatening complications.

Conflict of interest

None

Consent

This manuscript is written after obtaining written consent from the patient.

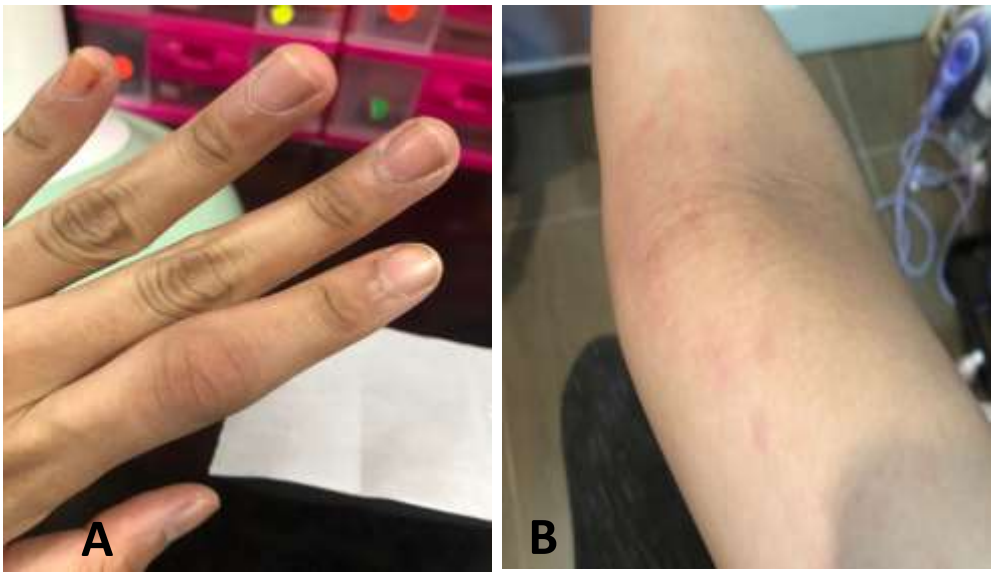

Figure 1. Active synovitis over the proximal interphalangeal joint of the left index finger (A) and the left knee joint (B).

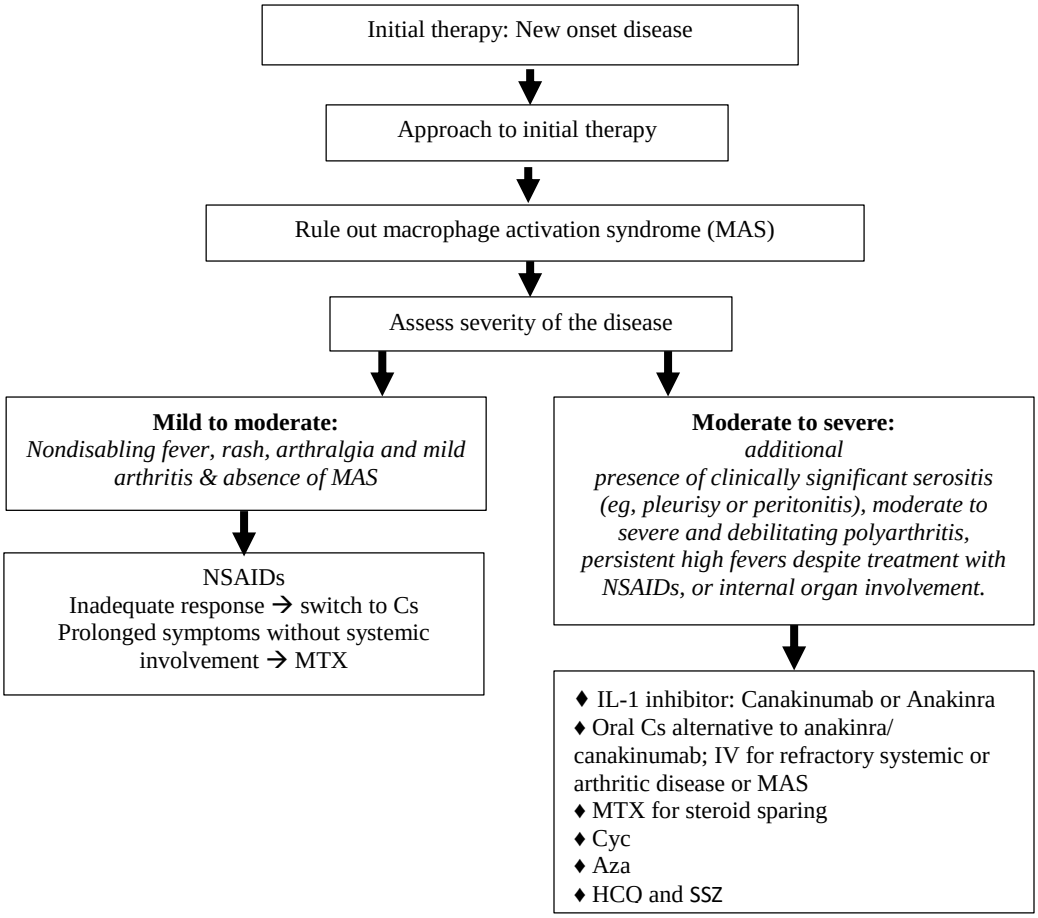

Figure 2. Summary of consensus of treatment of AOSD

MAS, macrophage activation syndrome; NSAIDs, non-steroidal anti-inflammatory drugs; Cs, corticosteroid; IL, interleukin; IV, intravenous; MTX, methotrexate; Cyc, cyclosporin; Aza, azathioprine; HCQ, hydroxychloroquine; SSZ, sulphasalazine.

Table 1. Laboratory results

Hematological, serological and biochemistry parameters	At presentation	4 weeks after treatment
Hb (g/dL)	8.5	11.0
PCV (%)	27	35
MCV (fL)	71	76
MCH (pg)	23	24
MCHC (g/dL)	32	31
WBC ($x10^9$/L)	21.3	9.3
Differential Count:		
Neutrophils (%)	87.1	55.0
Lymphocytes (%)	9.0	35.7
Neutrophils **(**$x10^9$/L)	18.6	5.1
PC **(**$x10^9$/L)	440	247
ESR **(**mm/hr)	128	33
CRP **(**mg/L)	219.4	2.0
Serum Albumin (g/L)	27	36
ANA	Positive 1:160 (Speckled)	-
Anti-dsDNA	Negative	-
p-ANCA, c-ANCA	Negative	-
ENA	Negative	-
Rheumatoid factor	Negative	-
Anti-CCP antibody	Negative	-
Serum Ferritin (ug/L)	3103.9	215.4
Serum Fibrinogen (g/L)	7.96	-
AST (U/L)	18	-
Triglyceride (mmol/L)	1.8	-
Mycobacterium TB Quantiferon	Indeterminate	-
Blood and urine culture and sensitivity	Negative	-

Abbreviation: Hb, hemoglobin; PCV, packed cell volume; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; WBC,white blood cell; PC, platelets; ESR, erythrocyte sedimentation rate; CRP, c-reactive protein; ANA, anti-nuclear antibody; dsDNA, double stranded DNA; p-, c-ANCA, perinuclear and cytoplasmic anti neutrophilic cytoplasmic antibodies; ENA, extractable nuclear antigen; anti-CCP ab, anti-citrullinated cyclic peptide; AST, aspartate transaminase; TB, tuberculosis.

Table 2. Yamaguchi's criteria for the diagnosis of adult-onset Still's disease.

Major criteria	Minor criteria	Exclusion criteria
Fever ≥ 39ºC lasting ≥ 1 week	Sore throat	Infection
Arthralgia or arthritis lasting ≥ 2 weeks	Lymphadenopathy	Malignancy
Typical non pruritic salmon-colored rash	Hepatosplenomegaly or Splenomegaly	Other rheumatic disease (vasculitis)
Leukocytosis ≥ 10 x 10^9/L with Neutrophil ≥ 80%	Abnormal liver function tests	
	Negative ANA and RF	

Notes: Diagnosis of AOSD if ≥ 5 criteria are present with ≥ 2 being major criteria and no exclusion criteria.[9]

Abbreviation: ANA, anti-nuclear antibody; RF, rheumatoid factor; AOSD, adult-onset Still's disease

References

[1]. Still GF. On a form of chronic joint disease in children. Med Chir Trans 1897; 80:47-60.9.

[2]. Bywaters EG. Still's disease in the adult. Ann Rheum Dis 1971;30(2):121–33.

[3]. Balci MA, Pamuk €ON, Pamuk GE, Uzundere FK, Donmez S. Epidemiology and outcome

[4]. of adult-onset Still's disease in Northwestern Thrace region in Turkey. Clin Exp Rheumatol 2015;33(6):818–23.

[5]. Wakai K, Ohta A, Tamakoshi A, Ohno Y, Kawamura T, Aoki R, et al. Estimated

[6]. prevalence and incidence of adult Still's disease: findings by a nationwide epidemiological

[7]. survey in Japan. J Epidemiol 1997;7(4):221–5.

[8]. Magadur-Joly G, Billaud E, Barrier JH, Pennec YL, Masson C, Renou P, et al. Epidemiology of adult Still's disease: estimate of the incidence by a retrospective study in west France. Ann Rheum Dis 1995;54(7):587–90.

[9]. Asanuma YF, Mimura T, Tsuboi H, Noma H, Miyoshi F, Yamamoto K, et al. Nationwide epidemiological survey of 169 patients with adult Still's disease in Japan. Mod Rheumatol 2015;25(3):393–400.

[10]. Efthimiou P, Kadavath S, Mehta B. Life-threatening complications of adult-onset Still's disease. Clin Rheumatol. 2014; 33:305-14

[11]. Petersdorf RG. Beeson PB. Fever of unexplained origin: report on 100 cases. Medicine (Baltimore) 1961; 40:1–30.

[12]. Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H et al. Preliminary criteria for classification of adult Still's disease. J Rheumatol. 1992;19(3): 424–430.

[13]. Fautrel B, Zing E, Golmard J-L, Le Moel G, Bissery A, Rioux C et al. Proposal for a new set of classification criteria for adult-onset Still disease. Medicine. 2002;81(3):194–200.

[14]. Mahroum N, Mahagna H, Amital H. Diagnosis and classification of adult Still's disease. J Autoimmun. 2014;48–49:34–37.

[15]. Gerfaud-Valentin M, Jamilloux Y, Iwaz J, Sève P. Adult-onset Still's disease. Autoimmun Rev. 2014;13(7):708–722.

[16]. McGonagle D, McDermott MF. A proposed classification of the immunological diseases. PLoS Med. 2006;3(8):e297.

[17]. Ekbote GS, L, Tanna D, Raval D, Negalur N, Kazi W, et al. Adult-onset Still's disease:

[18]. diagnosis of exclusion "still" rare, a retrospectve study on clinical profile and outcome at a tertary care center. Indian J Rheumatol 2018;13(6):S185

[19]. Fautrel B, Le Mo€el G, Saint-Marcoux B, Taupin P, Vignes S, Rozenberg S, et al. Diagnostic value of ferritin and glycosylated ferritin in adult-onset Still's disease. J Rheumatol 2001;28(2):322–9.

[20]. Sapkota A, Pokhrel N, Adhikari J, Shrestha B, Yadav YK. Adult-onset Still's Disease: A Case Report. JNMA J Nepal Med Assoc. 2020 Feb;58(222):115-118. doi: 10.31729/jnma.4844.

[21]. Patel S, Monemian S, Khalid A, Dosik H. Iron Deficiency Anemia in Adult-Onset Still's Disease with a Serum Ferritin of 26,387 μg/L. Anemia. 2011; 2011:184748. doi: 10.1155/2011/184748.

[22]. Wesam F, Olfa A, Soad A, Samira A, Mohamed F, Facharzt Feur I. Adult-Onset Still's Disease: Unusual Association! American Journal of Gastroenterology 2009;104: p S264

[23]. Emin, S, Boyadzhieva, V, Stoilov, N, Stoilov, R. Clinical case of a patient with adult-onset Still's disease – a diagnostic challenge or a late diagnosis? Rheumatology (Bulgaria) 2021;28(4):72-80. https://doi.org/10.35465/28.4.2020.pp72-80

[24]. Mollaeian A, Chen J, Chan NN, Nizialek GA, Hass CJ. Adult onset Still's disease in the elderly: a case-based literature review. BMC Rheumatol 2021; 5:12. https://doi.org/10.1186/s41927-021-00183-6

[25]. Lakshman H, Athwal PSS, Gondi A, Dhillon S, Towfiq BA. A Case of Adult-Onset Still's Disease with Positive Antinuclear Antibodies. Cureus. 2020;12(10): e10761. doi: 10.7759/cureus.10761.

[26]. Niranvichaiya S, Triwongwaranat D. Diagnostic Challenge: A Report of Two Adult-Onset Still's Disease Cases. Case Rep Dermatol Med. 2017; 2017:3768603. doi: 10.1155/2017/3768603.

[27]. Awad J, Farah R, Horn I. Adult Still's disease despite the presence of positive antinuclear antibodies. Eur J Intern Med. 2007;18(2):155-7. doi: 10.1016/j.ejim.2006.07.025.

[28]. Ravelli A, Minoia F, Davì S, Horne A, Bovis F, Pistorio A, Paediatric Rheumatology International Trials Organisation. Childhood Arthritis and Rheumatology Research Alliance. Pediatric Rheumatology Collaborative Study Group. Histiocyte Society et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European league against rheumatism/American college of rheumatology/paediatric rheumatology international Trials organisation collaborative Initiative. Ann Rheum Dis. 2016;75(3):481–489.

[29]. Fautrel B, Borget C, Rozenberg S, Meyer O, Le Loët X, Masson C, et al. Corticosteroid sparing effect of low dose methotrexate treatment in adult Still's disease. J Rheumatol. 1999;26(2):373–378.

[30]. Efthimiou P, Kontzias A, Hur P, Rodha K, Ramakrishna G, Nakasato P. Adult-Onset Still's Disease in Focus: Clinical Manifestations, Diagnosis, Treatment, and Unmet Needs in the Era of Targeted Therapies. Semin. Arthritis Rheum. 2021, 51, 858–874. [CrossRef]

[31]. Colafrancesco S, Manara M, Bortoluzzi A, Serban T, Bianchi G, Cantarini L et al. Correction to: Management of Adult-Onset Still's Disease with Interleukin-1 nhibitors: Evidence- and Consensus-Based Statements by a Panel of Italian Experts. Arthritis Res. Ther. 2020, 22, 6. [CrossRef]

[32]. Macovei LA, Burlui A, Bratoiu I, Rezus C, Cardoneanu A, Richter P et al. Adult-Onset Still's Disease—A Complex Disease, a Challenging Treatment. Int. J. Mol. Sci. 2022;23: 12810. https://doi.org/10.3390/ijms232112810

[33]. Ma Y, Meng J, Jia J, Wang M, Teng J, Zhu D, et al. Current and Emerging Biological Therapy in Adult-Onset Still's Disease. Rheumatology 2021; 60:3986–4000. [CrossRef]

[34]. Bagnari V, Colina M, Ciancio G, Govoni M, Trotta F. Adult-Onset Still's Disease. Rheumatol. Int. 2009; 30:855–862. [CrossRef]

[35]. Efthimiou P, Kontzias A, Ward C, Ogden N. Adult-Onset Still's Disease: Can Recent Advances in Our understanding of Its Pathogenesis Lead to Targeted Therapy? Nat. Rev. Rheumatol. 2007; 3:328–335. [CrossRef]

[36]. Tomaras S, Goetzke C, Kallinich T, Feist E. Adult-Onset Still's Disease: Clinical Aspects and Therapeutic Approach. J. Clin. Med. 2021; 10:733. [CrossRef]

[37]. Nordström D, Knight A, Luukkainen R, van Vollenhoven R, Rantalaiho V, Kajalainen A, 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(10):2008–2011.

[38]. Ortiz-Sanjuán F, Blanco R, Calvo-Rio V, Narvaez J, Rubio Romero E, Olivé A, 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(6):1659–1665.