CASE REPORT

Management of Adult-Onset Still's Disease Patients in Intensive Care Unit: A Case Report

Ika Jati Setya Andriani[✉*,**], Pradana Bayu Rakhmatjati[*], Calcarina Fitriani Retno Wisudarti[**], Untung Widodo[**]

[*]Department of Anesthesiology and Intensive Therapy, Faculty of Medicine, Diponegoro University/RSUP Dr. Kariadi, Semarang, Indonesia
[**]Department of Anesthesiology and Intensive Therapy, Gadjah Mada University/RSUP Dr. Sardjito, Yogyakarta, Indonesia

[✉]Correspondence: andriani.wibisono@gmail.com

ABSTRACT

Background: Adult-onset Still's disease (AOSD) is a rare inflammatory disorder characterized by the classic triad of fever, arthritis, and evanescent rash. AOSD is a multi-systemic disorder with unclear etiology. Glucocorticoids are the first line treatment for AOSD, and disease-modifying anti-rheumatic drugs (DMARDs) are often used in some patients with a poor response to glucocorticoids. Parenchymal lung involvement in AOSD is rare (only 5% of AOSD), one of them is acute respiratory distress syndrome (ARDS), where ARDS is the most severe complication. Management of such conditions in the intensive care unit (ICU) is crucial.

Case: A 25-year-old woman came with unresolved fever for one week which was preceded by joint pain and reddish spots on the skin. The patient was diagnosed as AOSD complicated with ARDS due to pneumonia which kept the patient in the ICU for 24 days.

Discussion: AOSD is a multigenic auto-inflammatory disorder involving the innate and adaptive immune systems. Based on Yamaguchi's criteria, the patient was diagnosed with AOSD where there was a high fever that lasted more than a week, arthritis, salmon rash, leucocytosis, sore throat, splenomegaly, alanine aminotransferase (ALT) abnormalities, and negative antinuclear antibodies (ANA) test. The first-line therapy given was methylprednisolone, doses were tapered gradually. As the patient didn't respond to therapy, she was then given immunosuppressive therapies such as cyclosporine, hydroxychloroquine and underwent therapeutic plasma exchange (TPE). The patients responded to treatments and showed good laboratory results.

Conclusion: This case report describes a patient with AOSD that was diagnosed based on clinical manifestations and Yamaguchi criteria. The patient improved clinically with high dose administration of corticosteroids, immunosuppressive agents, and TPE. Making a correct diagnosis and starting an appropriate treatment as soon as feasible is crucial in this case as the patient suffers complications.

Keywords: adult-onset Still's disease; ARDS; ICU; immunosuppresive; plasmapheresis

INTRODUCTION

Adult-onset Still's disease (AOSD) is a rare inflammatory disorder characterized by the classic triad of fever, arthritis, and a salmon-colored rash.[1] Epidemiological results suggest that the incidence of AOSD ranges between 0.16 and 0.4/100,000 people and the estimated prevalence is between 1 and 34 cases/1 million people. Although in some cases it is more common in women, AOSD is considered to be equally distributed between the two sexes. AOSD usually occurs in young adults with peak ages between 15-25 and 36-46 years. However, cases in old age, after the age of 60 years, have also been reported.[2]

Currently, AOSD is a multi-systemic disorder with an unknown etiology, viral infections, genetic factors, and immune dysregulation, including cytokine mediated inflammation and apoptosis dysregulation, all of which have been implicated in the development of this disease.

Glucocorticoids are the primary treatment in AOSD, and DMARDs are frequently used in some patients with poor response to glucocorticoids. Approximately 17-32% of AOSD patients are resistant to first-line corticosteroids and second-line DMARDs in some observational studies, or so-called 'refractory AOSD'. Currently, with the success of targeted biological treatments in rheumatic diseases, the management of AOSD has undergone a revolution.[3]

Lung parenchymal involvement in AOSD is rare (only in 5% of AOSD) and covers a wide spectrum, one of which is ARDS, of which ARDS is the most severe.[4,5] In this case, we will discuss AOSD patients with ARDS complications during treatment in the ICU.

CASE

A 25-year old woman came with complaints of fever that had been fluctuating for the past 7 days, which was preceded by pain in the muscles and joints and reddish spots appeared 10 days ago. Patients also complain of hair loss and glare when exposed to sunlight. The patient was suspected of having an autoimmune disease during previous hospital treatment and was then referred because there was no improvement. During the examination, the patient complained of swallowing pain like swallowing a thorn and blurred vision. Blood pressure 119/85 mmHg, heart rate 80 x/minute regular, adequate, respiratory rate 20 x/minute, body temperature 38.9^{o}C, and oxygen saturation 99% room air. Physical examination revealed conjunctival bleeding in both eyes, Mallampati II opened his mouth with 3 fingers, vesicular lung sounds. On abdominal examination, schuffner 1 splenomegaly was found. Edema was found in both lower extremities, and there was generalized erythema on the skin. On supporting examinations, an increase in serum glutamic pyruvic transaminase (SGPT) (114), hyponatremia (134 mEq/L), hypoalbumin (2.5 g/dL), increased creatine phosphokinase (CPK) (3193 u/L), increased c-reactive protein (CRP) (29.82 m g/dL), increased procalcitonin (0.44 ng/mL), increased ferritin levels (5805 mcg/L), negative ANA (33.1 units), pyuria, and hematuria.

On laboratory examination, leukocytosis (23,020/uL), hyperuricemia (62 mg/dL) and mild hyponatremia (134 mEq/L) were found. On blood gas analysis (BGA) examination, pH was 7.134, pCO2 76.3, HCO3- 25.0. Chest x-ray (15/01/22) (Figure 1) showed normal heart and lungs. Abdomen scan examination showed signs of suspicion

for cystitis and minimal ascites. Based on Yamaguchi criteria, the patient was diagnosed with adult-onset still's disease. The patient was given therapy including intravenous injection of triofusin 16 dpm, methylprednisolone injection 250 mg/12 hours, hydroxychloroquine 1x 200 mg, ampicillin sulbactam injection 1.5 grams/8 hours, paracetamol infuse 1g/8 hours, esomeprazole injection 40mg/24 hours, UDCA 250 mg/12 hours, and albumin correction 20%.

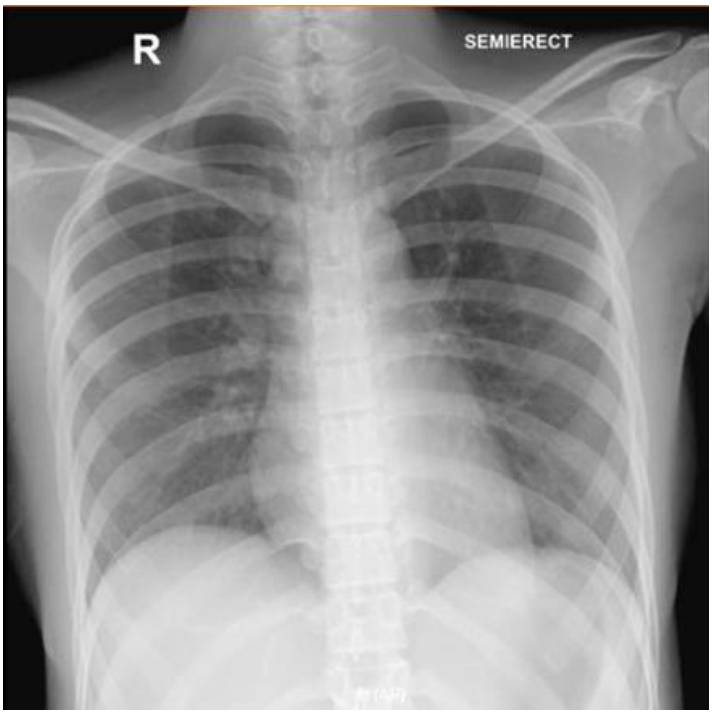

Figure 1. Chest X-Ray (15/01/22)

On the second day of treatment, the patient experienced worsening symptoms with decreased consciousness (GCS E1M1V1), blood pressure 85/62 mmHg, heart rate 117x/minute, respiratory rate 28x/minute fast and deep, temperature 37.4^{o}C, with saturation 87% with non-rebreathing mask 10 litre per minute (LPM). The patient was diagnosed with ARDS and then treated in the ICU.

On the first day in the ICU, the patient was intubated with a continuous positive airway pressure (CPAP) Pressure-support ventilation (PSV) Positive end expiratory pressure (PEEP) 8 FiO2 40% ventilator for indications of respiratory failure. BGA examination showed pH 7,131, pCO2 76.9, PO2 48, HCO3- 25.0. A days later the patient showed signs of pneumonia. The patient was given a norepinephrine injection of 0.005 mcg/kgbw/minute and the antibiotic therapy was changed to a levofloxacin injection of 750 mg/24 hours, a meropenem injection of 1 gr/8 hours, and a fluconazole injection of 200 mg/24 hours. After experiencing improvement in symptoms with glasgow coma score (GCS) E4M6Vett and SpO2 99% VM CPAP PSV peep 6 FiO2 40%. BGA results showed pH 7.421, pCO2 52.5, HCO3- 33.4. The patient was then extubated and replaced with high flow nasal cannula (HFNC) flow 40 FiO2 40%.

On the 9th day, the patient experienced worsening symptoms again with a general condition of severe pain and somnolence, blood pressure 130/71 mmHg, pulse 112x/minute, respiratory rate 17x/minute, temperature 38.5°C and SpO2 99% HFNC. The patient was then intubated again with a CPAP PSV PEEP 6 FiO2 50% ventilator mode. The results of the bronchoalveolar lavage (BAL) staining examination showed *Pneumocystis jirovecii* infection. Head multislice computed tomography (MSCT) examination showed lacunar infarcts in the right and left corona radiata, gyral enhancement in the right frontal region, as well as focal cerebral atrophy in the right and left frontal regions.

The patient was diagnosed with sepsis and pneumonia pneumocystis (PCP) so the therapy given was added to cotrimoxazole 960 mg and the addition of immunosuppressive drugs in the form of cyclosporine 25 mg/24 hours. The use of methylprednisolone injection was tapered off on the 4th day to 125 mg/12 hours, then to 62.5mg/12 hours on the 7th day. On the 10th day the patient was able to contact and communicate, but still appeared short of breath. On chest x-ray (25/01/22) (Figure 2) it showed improvement and appearance of pulmonary edema, possibly accompanied by bronchopneumonia with reduced infiltrates.

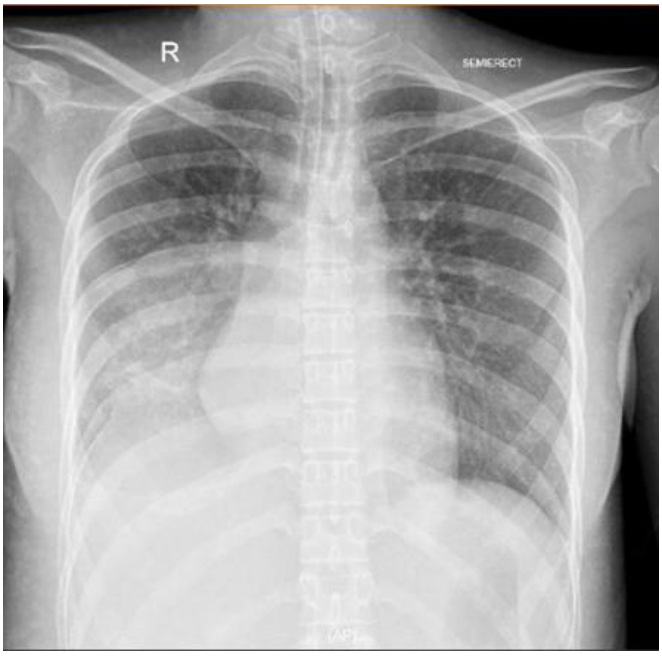

Figure 2. Chest X-Ray (25/01/22)

The patient began TPE therapy with a plan of 4 times. The patient experienced improvement in symptoms. However, on day 15, the patient underwent percutaneous dilatational tracheostomy (PDT) with SIMV PEEP 5 FiO2 60% oxygen therapy. On the 24th day, the patient's condition began to improve, patient was conscious, with vital signs within normal limits and BGA results were good. The patient is then programmed to move to a regular treatment room.

DISCUSSION

Adult-onset Still's disease (AOSD) is a multigenic auto-inflammatory disorder at the crossroads of auto-inflammatory and autoimmune diseases due to its complex pathogenesis, involving both innate and adaptive immune system.

It is generally accepted that unknown factors, acting as second hit, may trigger a pathologic process in genetically susceptible patients finally leading to the activation of an aberrant inflammatory response, which is responsible of AOSD development. Environmental signals (pathogen-associated molecular patterns, PAMPs; or danger-associated molecular patterns, DAMPs) set fire to the innate immune receptors (Toll-like receptors, TLRs; or Nod-like receptors, NLRs), which in turn trigger the activation and secretion of inflammatory cytokines (i.e., IL-1b, IL-18, IL-6), then adaptive immune cells such as Th1 and Th17 also play a role. This cytokine plays a role in the emergence of clinical manifestations in AOSD.[1,2]

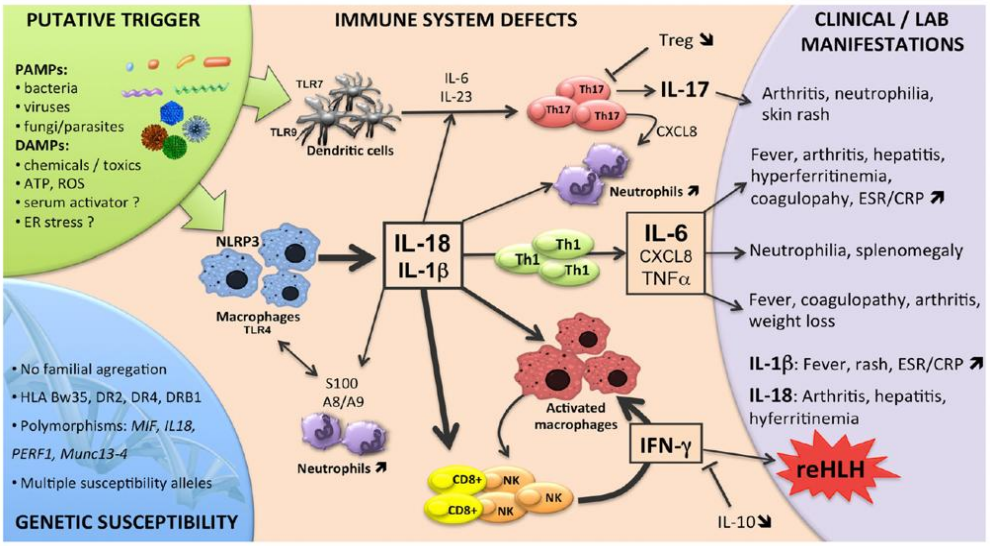

Figure 3. Pathogenesis of adult-onset Still's disease

Clinically, there are classic manifestations of AOSD, including fever (93-100%), arthritis (86-100%), skin rash (58-87%), and other symptoms such as myalgia (13–84%), splenomegaly (35–79%), lymphadenopathy *(2* 8–74%), sore throat (27–74%), and kidney involvement (21–62%).[2] The clinical course of AOSD can be categorized into two patterns, including systemic articular pattern and chronic articular pattern. In patients with a systemic pattern, the course of the disease usually lasts only a few weeks to months and the dominant clinical symptoms are fever, rash, serositis and hepatosplenomegaly. Patients with a chronic pattern of the pattern have a persistently active disease course in which articular symptoms predominate.[6] In the reported case, the patient had several clinical manifestations in the form of classic manifestations as well as splenomegaly and sore throat. Based on normal laboratory examination, it will show an increase in CRP (96-100%) and erythrocyte sedimentation rate (ESR) (87-99%), neutrophilic leukocytosis (74-94%), inflammatory anemia (18-68%). Elevated ALT levels (36-74%) can also generally be experienced as well as hyperferritinemia (69-93%).

Serum ferritin levels were observed to be higher than in other autoimmune, inflammatory, infectious or neoplastic diseases, characterized by a decrease in glycosylated ferritin (<20%). Despite poor specificity, a 5-fold increase in serum ferritin levels is highly suggestive of AOSD and is generally considered a useful marker to assess disease activity and to predict the occurrence of macrophage activation syndrome (MAS).[2] Antinuclear antibodies (ANA) and rheumatoid factor (RF) were mostly found to be negative (in 100% and 95% of patients, respectively). Elevated serum levels of interleukin-6, *tumor* necrosis factor, interferon gamma and interleukin-18 may be found, but these tests are not specific for AOSD.

The diagnosis of AOSD is generally made clinically because there is no definitive supporting examination. Apart from that, other examinations are also needed to rule out differential diagnoses such as infections, autoimmune diseases, inflammatory diseases, or neoplasms that have characteristics similar to AOSD. Several diagnostic criteria have been proposed to establish the diagnosis of AOSD. These criteria are based on a combination of clinical and laboratory findings. One of the diagnostic criteria used is the Yamaguchi criteria which consists of major and minor criteria (Table 1). This criterion requires 5 or more criteria including 2 or more major criteria to be diagnosed with AOSD (sensitivity 96.2% and specificity 92.1%).[7]

Table 1. Criteria for the diagnosis of adult-onset Still's disease

Major criteria	Fever ≥ 39°C lasting ≥ 1 week
	Arthralgia or arthritis lasting ≥ 2 weeks
	Typical nonpruritic salmon-colored rash
	Leukocytosis ≥ 10,000/mm^3 with granulocytes ≥ 80%
Minor criteria	Sore throat
	Lymphadenopathy
	Splenomegaly
	Abnormal liver function tests
	Negative tests for antinuclear antibody and rheumatoid factor
Exclusion criteria	Infection
	Malignancy
	Other rheumatic disease (vasculitis)

Notes: Diagnosis of adult-onset Still's disease if ≥ 5 criteria are present with ≥ 2 being major criteria and no exclusion criteria. Data from.[7]

Based on the case above, the patient met several criteria, namely high fever that lasted more than a week, arthritis, salmon rash, leukocytosis, sore throat, splenomegaly, ALT abnormalities, and negative ANA.

The first line of AOSD therapy is to use corticosteroids, regardless of the clinical manifestations the patient has. However, the use of corticosteroids sometimes causes dependence and is often associated with splenomegaly, low ferritin glycosylated levels, increased ESR levels, and early onset AOSD.

Therefore, if the patient meets these criteria, a steroid sparing agent needs to be given. If the first line does not provide improvement, disease-modifying anti-rheumatic drugs (DMARDS) therapy can be given, such as cyclosporine A, leflunomide, azathioprine, hydroxychloroquine, D-penicillamine,

and tacrolimus. If the patient is resistant to first and second line treatment, or better known as refractory AOSD, then they need to be given biological agent therapy such as anti tumor necrosis factor alpha (TNF-α), IL-1 antagonist.[8] The patient in this case used methylprednisolone as first line therapy, but because it did not cause improvement, second line therapy was added in the form of cyclosporine and hydroxychloroquine.

Based on the patient's BGA results on the first day of treatment in the ICU, the patient was intubated with a CPAP PSV PEEP 8 FiO2 40% ventilator mode for indications of respiratory failure. Respiratory failure consists of 2 types, namely 1) Type 1 (hypoxemia) which is characterized by PaO2 < 60 mmHg with normal or decreased PaCO2, and 2) Type 2 (hypercarbia) with PaCO2 > 45 mmHg and pH < 7.35. BGA examination αshowed pH 7,131, pCO2 76.9, PO2 48, HCO3- 25.0 so the patient was classified as type 2 respiratory failure. BGA changes during treatment in the ICU can be seen in a graphic (Figure 4) along with the respiration rate in vital sign chart (Figure 5).

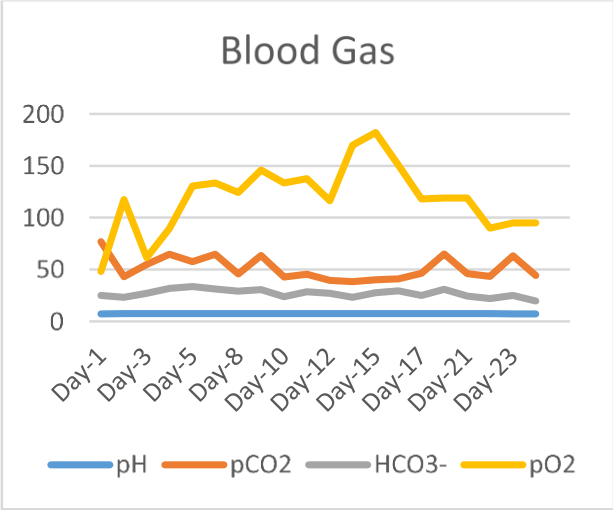

Figure 4. Blood gas analysis chart

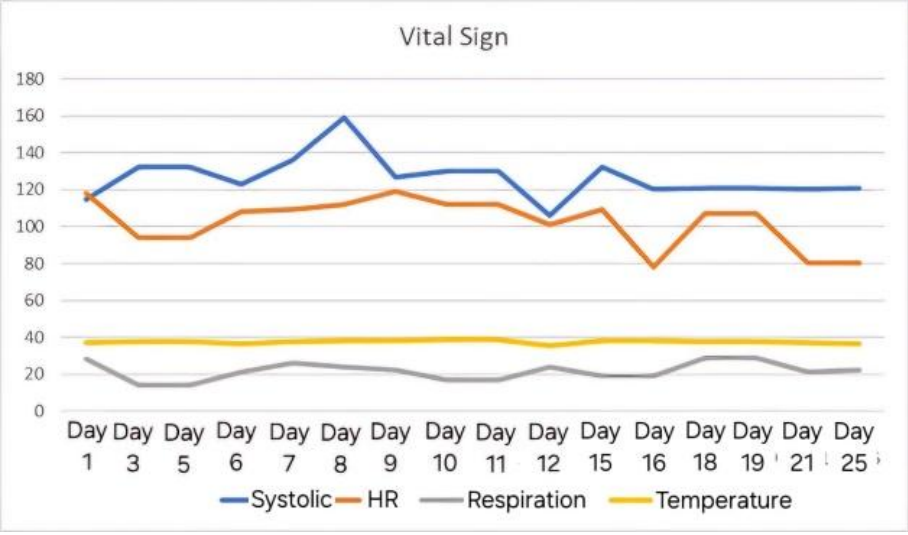

Figure 5. Vital sign chart

Respiratory failure can occur due to respiratory tract infections or due to AOSD. In this case, the patient was initially diagnosed with ARDS with a showing signs of pneumonia. The patient then experienced respiratory failure and after staining for lactic acid bacteria fungus, the results showed positive *Pneumocystis jirovecii*. Therefore, the patient was given the drug cotrimoxazole, which until now was declared a first-line drug for pneumocystis pneumonia (PCP) and the patient's condition improved clinically and in terms of chest X-rays.[9] During 24 days of treatment in the ICU, the patient often experienced several episodes of respiratory failure so he was intubated twice with a ventilator installed and then PDT was performed.

The number of cases reported in the literature of pulmonary parenchymal involvement (PLI) in AOSD is very small. PLIs in AOSD can be divided into two main categories: one with ARDS and one with other PLIs. In the case series of Mathieu Gerfaud-Valentin et al., ARDS occurred in 40% of patients with moderate-severe AOSD and PLI. ARDS is considered an early complication of AOSD, because it occurs mainly within the first year from diagnosis. In addition, ARDS is the main cause of death in AOSD-related PLI.[10]

There are currently no specific guidelines regarding the management of ARDS in AOSD patients, so the therapy given is supportive therapy. According to research, corticosteroid therapy as first line appears to be a reasonable option. In case of corticosteroid failure, physicians should consider initiating treatment with an IL-1 receptor antagonist (anakinra) or with a humanized anti-IL-6 receptor antibody (tocilizumab).[11]

During treatment, the patient experienced improvement in symptoms after being given immunosuppressive therapy and TPE. Plasma exchange (TPE) is an extracorporeal blood purification procedure that can remove part or all of pathogenic substances from the blood, such as various toxic substances, immunoglobulins (Igs), various circulating auto-antibodies and immune complexes and, then, replace the separated plasma with fluid. surrogates, including fresh frozen plasma (FFP) or certain concentrations of human albumin via centrifugal or membrane filtration devices.

TPE has been widely applied in a variety of conditions, including neurological disorders, hematology, nephrology, dermatology, and even rheumatism. According to research by Bai Z, et al., the most common indication for TPE was systemic lupus erythematosus (SLE), accounting for 50.2%. TPE is performed in SLE patients suffering from lupus crisis, lupus nephritis, or in severe disease activity. Other main indications for TPE were dermatomyositis/polymyositis (13%), Sjögren's syndrome (7%), and overlap syndrome (6%). Other relatively rare indications of TPE include adult-onset Still's Disease (4%), connective tissue disease (4%), antineutrophil cytoplasmic associated vasculitis (4%), IgG4 associated disease (3%), systemic sclerosis (3%), antiphospholipid syndrome (3%), rheumatoid arthritis (1%), hemophagocytic syndrome (1%), and systemic vasculitis (1%).

Of the 12 AOSD patients who were given TPE in the study, 1 patient (8.3%) experienced complete remission, 8 patients (66.7%) experienced partial remission, and 3 patients (25%) experienced worsening/persistence. The

Complete remission was defined as normal laboratory examinations without clinical symptoms. The partial remission was defined as the achievement of laboratory indices improving up to at least 50%, compared to baseline and no occurrence of new clinical symptoms. Persistence/worsening was referred to a persistent/deteriorated condition of the laboratory indices and clinical symptoms. From the results of this study it can be concluded that more than 50% of patients experienced improvement after receiving TPE. This may be due to the involvement of TPE in the pathophysiology of the disease by eliminating autoantibodies and reducing the amount of elevated cytokines.[12]

Research by Ito T, et al. also showed similar results. In that study, patients with AOSD with liver involvement were given cyclosporine but did not experience improvement. The patient was then given TPE because the cytokine results were 40 units of FFP 6 times (2 times/week for 3 weeks) and the patient's laboratory results improved dramatically. The patient's cytokines had previously increased, then decreased. The decrease in cytokines may be due to the TPE mechanism in resetting hypercytokinemia which causes the patient's condition to worsen.[13] In this case, the patient underwent TPE 4 times and gave good results. This is indicated by an improvement in the general condition and no new clinical symptoms appearing.

Although TPE has been widely applied in AOSD patients, new treatment methodes and composite biomarkers are still required to improved the result of patients with AOSD by recognizing disease pathophysiology properly.[14] Early acknowledgment also plays an urgent part; in this way, patients ought to be taught on the trademark signs and side effects of AOSD, including persistent fevers, rash, and joint pain. Empower patients to look for medical attention in case they encounter such signs could be a good early step to do.[15]

CONCLUSION

The case report describes a patient with AOSD complicated by ARDS. Patients was diagnosed based on clinical manifestations and the results of supporting examinations using the Yamaguchi criteria. The patient improved clinically with high doses administration of corticosteroids, immunosuppressive agents, and TPE. Making a correct diagnosis and starting an appropriate treatment as soon as feasible is crucial in this case as the patient suffered complication.

REFERENCES

1. Jamilloux Y, Gerfaud-Valentin M, Martinon F, Belot A, Henry T, Sève P. Pathogenesis of adult-onset Still's disease: new insights from the juvenile counterpart. Immunol Res. 2015 Feb 1;61(1–2):53–62.
2. Giacomelli R, Ruscitti P, Shoenfeld Y. A comprehensive review on adult onset Still's disease. Vol. 93, Journal of Autoimmunity. Academic Press; 2018. p. 24–36.
3. 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. Vol. 60, Rheumatology (Bulgaria). Medical Information Center; 2021. p. 3986–4000.
4. Mitrovic S, Fautrel B. Complications of adult-onset Still's disease and their management. Vol. 14, Expert Review of Clinical Immunology. Taylor and Francis Ltd; 2018. p. 351–65.

5. Gerfaud-Valentin M, Cottin V, Jamilloux Y, Hot A, Gaillard-Coadon A, Durieu I, et al. Parenchymal lung involvement in adult-onset Still disease: A STROBE-compliant case series and literature review. Vol. 95, Medicine (United States). Lippincott Williams and Wilkins; 2016.
6. Selvaratnam N, Srivickneswaran G, Thananchayan S, Uthayakumaran S, Muthulingam A. A parenchymal lung involvement in a patient with adult-onset of Still's disease: a rare case report. Journal of the Postgraduate Institute of Medicine. 2021 Nov 29;8(2):160.
7. Mahroum N, Mahagna H, Amital H. Diagnosis and classification of adult Still's disease. J Autoimmun. 2014;48–49:34–7.
8. Jamilloux Y, Gerfaud-Valentin M, Henry T, Sève P. Treatment of adult-onset still's disease: A review. Vol. 11, Therapeutics and Clinical Risk Management. Dove Medical Press Ltd.; 2014. p. 33–43.
9. Truong J, Ashurst JV. Pneumocystis Jirovecii Pneumonia. StatPearls. 2023 Jan 21;
10. Guerrieri A, Angeletti G, Mazzolini M, Bassi I, Nava S. Pulmonary involvement in adult Still's disease: Case report and brief review of literature. Respir Med Case Rep. 2017;22:91–4.
11. Xi XT, Wang MJ, Huang RY, Ding BH. Adult onset still's disease accompanied by acute respiratory distress syndrome: A case report. Exp Ther Med. 2016 Sep 1;12(3):1817–21.
12. Bai Z, Chen Y, Dong L. Experience of therapeutic plasma exchange in rheumatic diseases: Albumin may be a suitable substitute for plasma. Arch Rheumatol. 2021;36(3):398–408.
13. Ito T, Ozaki Y, Shimamoto K, Amuro H, Tanijiri T, Yokoi T, et al. Successful treatment with plasma exchange in adult-onset Still's disease with hyper-IL-18-naemia and hyperallergic state. Mod Rheumatol. 2008;18(4):407–10.
14. Yoo DH. Treatment of adult-onset still's disease: up to date. Expert Rev Clin Immunol. 2017 Sep;13(9):849-866. doi: 10.1080/1744666X.2017.1332994. Epub 2017 Jun 5. PMID: 28540751
15. Bhargava J, Panginikkod S. Still Disease. [Updated 2024 Feb 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538345/