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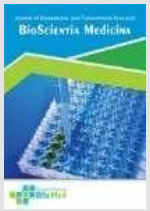

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A Rare Case of Adult-Onset Still's Disease Presenting with Hypercoagulability and Ocular Vasculitis

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A B S T R A C T

Background: Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory disorder characterized by fever, arthritis, rash, and hyperferritinemia. While AOSD commonly presents with systemic and articular manifestations, it can rarely involve other organ systems, including the eye and the coagulation system. **Case presentation:** We present a case of an 18-year-old male with AOSD who developed hypercoagulability and ocular vasculitis. The patient presented with high-grade fever, polyarthritis, and the characteristic salmon-pink rash. Laboratory investigations revealed leukocytosis, elevated inflammatory markers, and a significant elevation of serum ferritin. Imaging studies ruled out other diagnoses. During the course of his illness, the patient developed hematomas and was found to have elevated fibrinogen and D-dimer levels, suggestive of hypercoagulability. He also experienced ocular symptoms and was diagnosed with ocular vasculitis. The patient was treated with systemic corticosteroids, methotrexate, and anticoagulation therapy, which led to the resolution of his symptoms. **Conclusion:** This case highlights the rare and serious complications of AOSD, including hypercoagulability and ocular vasculitis. Early recognition and prompt treatment are crucial to prevent morbidity and mortality associated with these complications.

1. Introduction

Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory disorder that affects young adults, characterized by a classic triad of high-spiking fever, evanescent salmon-pink rash, and arthritis. The disease's etiology remains unknown, but it is believed to be triggered by a combination of genetic and environmental factors. AOSD presents a diagnostic challenge due to its wide range of clinical manifestations, often mimicking other conditions. Diagnosis relies on clinical findings and the exclusion of other diseases, with several diagnostic criteria proposed, including the Yamaguchi criteria, commonly used in clinical practice. AOSD commonly presents with systemic and articular manifestations, including sore throat, lymphadenopathy, hepatosplenomegaly, and serositis. The systemic inflammation associated with AOSD can lead to a cytokine storm, characterized by the release of pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). These cytokines play a crucial role in the pathogenesis of AOSD, contributing to the development of fever, rash, arthritis, and other systemic manifestations.[1-4]

While AOSD primarily affects the joints and systemic systems, it can rarely involve other organs, including the eye, heart, lungs, kidneys, and nervous system. Ocular involvement in AOSD is rare but can lead to significant morbidity if left untreated. The most

common ocular manifestation is anterior uveitis, characterized by pain, redness, photophobia, and blurred vision. Other ocular manifestations include keratitis, episcleritis, scleritis, and retinal vasculitis. Hypercoagulability is another rare but serious complication of AOSD, characterized by an increased tendency to form blood clots. This can lead to thromboembolic events such as deep vein thrombosis, pulmonary embolism, and stroke. The exact mechanism of hypercoagulability in AOSD is not fully understood but is thought to be related to systemic inflammation and activation of the coagulation cascade.[5-7]

The diagnosis of AOSD can be challenging due to its variable clinical presentation and the lack of specific diagnostic tests. AOSD can mimic various other conditions, including infections, malignancies, and other autoimmune diseases. The diagnosis is often made based on clinical findings, laboratory investigations, and exclusion of other conditions. Early recognition and prompt treatment of AOSD are crucial to prevent morbidity and mortality associated with the disease and its complications. Systemic corticosteroids are the mainstay of treatment for AOSD, helping control systemic inflammation and prevent further complications. Disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, can be used as steroid-sparing agents and help maintain remission. Anticoagulation therapy is essential to prevent thromboembolic events in patients with hypercoagulability.[8-10] In this report, we present a case of an 18-year-old male with AOSD who developed hypercoagulability and ocular vasculitis.

2. Case Presentation

An 18-year-old male student from Bengkulu, Indonesia, presented with a 3-day history of worsening joint pain and high-grade fever. The joint pain initially started in his thighs and ankles two weeks prior, gradually spreading to involve his shoulders, wrists, fingers, knees, and ankles. The fever was intermittent, reaching up to 39°C, and accompanied by chills and night sweats. He denied any sore throat, cough, rash, or weight loss. The patient had a history of rheumatic fever at age 9, which was treated for 10 years. He had stopped taking the medications for rheumatic fever a month before his current symptoms began. There was no family history of autoimmune diseases. He was a non-smoker and did not use intravenous drugs. On physical examination, he appeared unwell and had a fever of 38.1°C. He had a rapid heart rate (128 bpm) and rapid breathing (20 breaths/min), with a blood pressure of 130/70 mmHg. There were no swollen lymph nodes or enlarged spleen or liver. A distinctive salmon-pink rash was observed on his right upper arm, and he had bruises on his hands and feet. Several joints were tender and had limited movement. Laboratory tests revealed an elevated white blood cell count (12,620/mm3), a high erythrocyte sedimentation rate (ESR) (120 mm/hr), and elevated C-reactive protein (CRP) (116.7 mg/L). Liver function tests showed slightly elevated aspartate aminotransferase (AST) (40 U/L) and alanine aminotransferase (ALT) (49 U/L). Importantly, his serum ferritin level was markedly elevated at 801.6 ng/mL. Tests for antinuclear antibodies (ANA) and rheumatoid factor (RF) were negative. Coagulation studies showed a shortened prothrombin time (PT) (14.2 seconds), shortened activated partial thromboplastin time (APTT) (30.7 seconds), elevated fibrinogen (767 mg/dL), and elevated D-dimer (2.42 µg/mL). An electrocardiogram (ECG) revealed sinus tachycardia. Chest X-ray was normal. An echocardiogram showed normal heart function with no signs of pericarditis or valvular abnormalities. An ophthalmological examination revealed anterior uveitis and retinal vasculitis. Considering the patient's clinical presentation, laboratory results, and imaging studies, a diagnosis of adult-onset Still's disease (AOSD) was made, with complications of hypercoagulability and ocular vasculitis (Table 1).

The initial management of the patient's condition involved intravenous fluids such as Ringer's lactate to maintain hydration and electrolyte balance. Nonsteroidal anti-inflammatory drugs (NSAIDs), specifically ibuprofen 400 mg three times daily, were

administered to reduce inflammation and alleviate pain. Systemic corticosteroids, in the form of methylprednisolone 8 mg three times daily, were initiated to suppress the systemic inflammation associated with AOSD. Anticoagulation therapy with enoxaparin 0.6 mg subcutaneously twice daily was also commenced to address the hypercoagulable state and prevent thromboembolic events. Throughout this initial management phase, close monitoring of vital signs, including temperature, heart rate, and blood pressure, was essential. Regular assessments of joint pain and swelling were conducted to evaluate the response to treatment. Laboratory parameters, including complete blood count, ESR, CRP, ferritin, liver function tests, and coagulation profile, were closely monitored to assess disease activity and treatment efficacy. The patient was also vigilantly observed for any signs of bleeding or thromboembolic events, given the anticoagulation therapy. To address the ocular vasculitis, topical corticosteroids, such as prednisolone acetate 1% eye drops, were prescribed to reduce inflammation in the eyes. Cycloplegics, specifically cyclopentolate 1% eye drops, were also administered to temporarily paralyze the ciliary muscle and dilate the pupil, relieving pain and preventing complications such as synechiae formation. Regular ophthalmological examinations were scheduled to assess the severity of inflammation and the response to treatment, with careful monitoring for any changes in vision. Maintenance therapy involved transitioning the patient to oral corticosteroids, specifically prednisolone, with a tapering dose based on clinical response. Disease-modifying antirheumatic drugs (DMARDs) were introduced, with methotrexate 7.5 mg once weekly and folic acid 5 mg once weekly, to further control disease activity and reduce the reliance on corticosteroids. Regular follow-up with the rheumatology clinic was established to monitor disease activity, adjust treatment as needed, and assess for potential drug toxicity. Patient education emphasized the importance of medication adherence and awareness of potential side effects. Long-term follow-up included regular visits to both rheumatology and ophthalmology clinics, along with periodic laboratory monitoring to assess disease activity and overall health. Lifestyle modifications were encouraged, including regular exercise, a balanced diet, and stress management techniques, to promote well-being. Continued monitoring for disease flares and potential complications remained crucial, with adjustments to treatment as needed. Ongoing patient education and support were provided to ensure optimal disease management and quality of life (Table 2).

Table 1. Summary of patient's clinical presentation, investigations, and diagnosis.

Feature	Details
Demographics	18-year-old male, student, residing in Bengkulu, Indonesia
Presenting complaints	- Worsening joint pain (3 days); - High-grade fever (3 days)
History of presenting illness	- Initially, pain in thighs and ankles (2 weeks prior); - Pain progressed to involve shoulders, wrists, fingers, knees, and ankles; - Fever intermittent, up to 39°C, with chills and night sweats; - No sore throat, cough, rash, or weight loss
Past medical history	- Rheumatic fever at age 9 (treated for 10 years); - Discontinuation of medications 1 month prior
Family history	No family history of autoimmune diseases
Social history	Non-smoker, no history of intravenous drug use
Physical examination	- Unwell appearance; - Febrile (38.1°C); - Tachycardia (128 bpm); - Tachypnea (20 breaths/min); - BP 130/70 mmHg; - No lymphadenopathy or hepatosplenomegaly; - Salmon-pink rash on right upper arm (Figure 1); - Hematomas on hands and feet; - Tenderness and limited range of motion in multiple joints
Laboratory investigations	- Leukocytosis (WBC 12,620/mm3); - Elevated ESR (120 mm/hr); - Elevated CRP (116.7 mg/L); - Mildly elevated AST (40 U/L) and ALT (49 U/L); - Markedly elevated serum ferritin (801.6 ng/mL); - ANA and RF negative; - Shortened PT (14.2 seconds); - Shortened APTT (30.7 seconds); - Elevated fibrinogen (767 mg/dL); - Elevated D-dimer (2.42 µg/mL)
Imaging studies	- ECG: Sinus tachycardia; - Chest X-ray: Normal; - Echocardiogram: Normal cardiac function, no pericarditis or valvular abnormalities
Ophthalmological examination	- Anterior uveitis; - Retinal vasculitis
Clinical diagnosis	- Adult-onset Still's disease (AOSD); - Hypercoagulability; - Ocular vasculitis

Table 2. Treatment and follow-up.

Phase	Treatment	Monitoring and follow-up
Initial management	- Intravenous fluids (e.g., Ringer's lactate); - Nonsteroidal anti-inflammatory drugs (NSAIDs): Ibuprofen 400 mg three times daily; - Systemic corticosteroids: Methylprednisolone 8 mg three times daily; - Anticoagulation: Enoxaparin 0.6 mg subcutaneously twice daily	- Close monitoring of vital signs, including temperature, heart rate, and blood pressure; - Regular assessment of joint pain and swelling; - Monitoring of laboratory parameters, including complete blood count, ESR, CRP, ferritin, liver function tests, and coagulation profile; - Watch for signs of bleeding or thromboembolic events
Ocular vasculitis management	- Topical corticosteroids (e.g., prednisolone acetate 1% eye drops); - Cycloplegics (e.g., cyclopentolate 1% eye drops)	- Regular ophthalmological examinations to assess the severity of inflammation and response to treatment; - Monitoring for any changes in vision
Maintenance therapy	- Oral corticosteroids: Prednisolone (tapering dose based on clinical response); - Disease-modifying antirheumatic drugs (DMARDs): Methotrexate 7.5 mg once weekly with folic acid 5 mg once weekly	- Regular follow-up with rheumatology clinic to monitor disease activity and adjust treatment as needed; - Periodic laboratory monitoring to assess for drug toxicity and disease activity; - Patient education on the importance of medication adherence and potential side effects
Long-term follow-up	- Regular follow-up with rheumatology and ophthalmology clinics; - Periodic laboratory monitoring; - Lifestyle modifications to promote overall health and well-being, including regular exercise, balanced diet, and stress management	- Monitoring for disease flares and complications; - Assessment of treatment efficacy and adjustment as needed; - Patient education and support

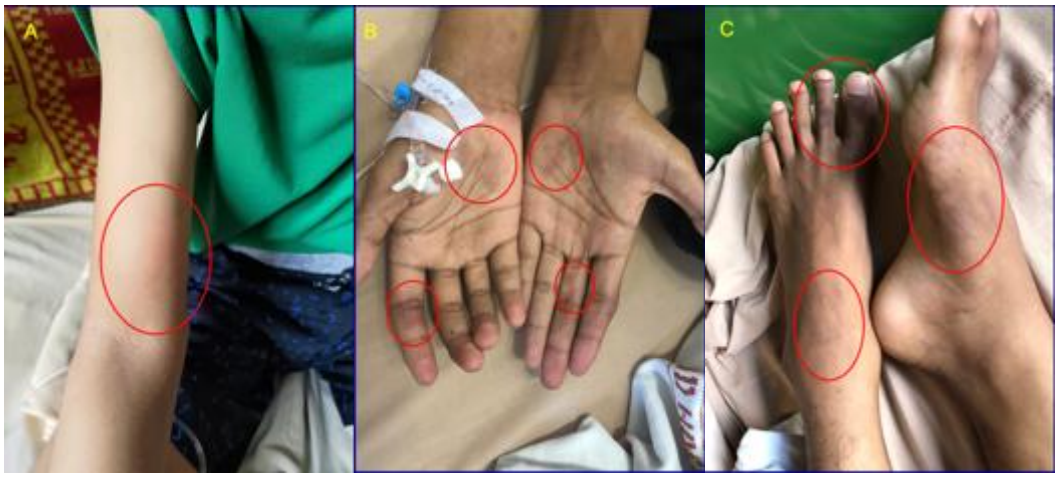

Figure 1. A. Salmon skin rash regio brachii dextra, B. Hematom regio manus dextra et sinistra, C. Hematome regio pedis dextra et sinistra.

3. Discussion

Adult-onset Still's disease (AOSD) presents a formidable diagnostic challenge due to its diverse clinical manifestations and the absence of pathognomonic laboratory or imaging markers. The disease can mimic various other conditions, including infections, malignancies, and other autoimmune diseases, making it a diagnosis of exclusion. The clinical presentation of AOSD is highly variable, ranging from mild and self-limiting to severe and life-threatening. The classic triad of high-spiking fever, evanescent salmon-pink rash, and arthritis is present in only a minority of patients. Other common manifestations include sore throat, lymphadenopathy,

hepatosplenomegaly, and serositis. However, these features are not specific to AOSD and can be seen in various other conditions. The protean nature of AOSD often leads to initial misdiagnosis or delayed diagnosis. The disease can mimic infections, such as sepsis or viral illnesses, particularly in patients presenting with fever and leukocytosis. The presence of arthralgia or arthritis can raise suspicion for other rheumatic diseases, such as rheumatoid arthritis or systemic lupus erythematosus. The systemic inflammation associated with AOSD can also mimic malignancy, particularly lymphoma or leukemia. Further complicating the diagnostic process are atypical presentations of AOSD, which can deviate significantly from the classic triad. These atypical presentations may include prominent pulmonary involvement, cardiac manifestations, neurological symptoms, or predominant gastrointestinal symptoms. Such presentations can easily mislead clinicians towards alternative diagnoses, leading to delays in appropriate treatment. Adding to the complexity, AOSD can share clinical features with other autoimmune and autoinflammatory diseases. For example, the fever and rash in AOSD can resemble those seen in systemic lupus erythematosus (SLE), while the arthritis can mimic rheumatoid arthritis (RA). Distinguishing AOSD from these overlapping conditions requires careful consideration of the overall clinical picture, including laboratory findings, imaging studies, and response to treatment. Diagnosing AOSD in pediatric and geriatric populations presents additional challenges. In children, AOSD can be mistaken for systemic juvenile idiopathic arthritis (sJIA), which shares similar clinical features. In older adults, AOSD may be overlooked or misdiagnosed as other age-related conditions, such as polymyalgia rheumatica or infection. There is no single diagnostic test for AOSD. Laboratory investigations often reveal non-specific findings, such as elevated inflammatory markers (e.g., erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]), leukocytosis, and hyperferritinemia. However, these findings are not unique to AOSD and can be seen in various other inflammatory conditions. Elevated ESR and CRP are common laboratory findings in AOSD, reflecting the underlying systemic inflammation. However, these markers are not specific to AOSD and can be elevated in various other conditions, including infections, malignancies, and other autoimmune diseases. Hyperferritinemia, or elevated serum ferritin levels, is a hallmark of AOSD. However, hyperferritinemia is not specific to AOSD and can be seen in other conditions, such as infections, malignancies, and hemophagocytic lymphohistiocytosis (HLH). Other non-specific laboratory findings in AOSD may include leukocytosis, anemia, thrombocytosis, and elevated liver enzymes. These findings can further complicate the diagnostic process, as they can be seen in various other conditions. Imaging studies, such as chest X-ray, computed tomography (CT) scan, and magnetic resonance imaging (MRI), are primarily used to exclude other diagnoses or assess for complications of AOSD. They rarely provide specific findings suggestive of AOSD. Several diagnostic criteria have been proposed for AOSD, including the Yamaguchi criteria, Fautrel criteria, and Cush criteria. These criteria are based on a combination of clinical and laboratory features, but none are universally accepted or entirely sensitive and specific. The Yamaguchi criteria are the most widely used criteria for AOSD. They include fever, arthralgia or arthritis, typical rash, leukocytosis, sore throat, lymphadenopathy, hepatosplenomegaly, and negative antinuclear antibody (ANA) and rheumatoid factor (RF). However, these criteria have been criticized for their low sensitivity, particularly in patients with atypical presentations. The Fautrel criteria are more recent criteria that include fever, arthralgia or arthritis, typical rash, hyperferritinemia, and exclusion of other diagnoses. These criteria have been shown to have higher sensitivity than the Yamaguchi criteria, but they may still miss some cases of AOSD. The Cush criteria are less commonly used criteria that include fever, rash, arthritis, leukocytosis, and elevated ESR. These criteria are relatively simple to apply, but they may not be as sensitive or specific as the Yamaguchi

or Fautrel criteria. All of the existing diagnostic criteria for AOSD have limitations. None are universally accepted or entirely sensitive and specific. The choice of criteria may depend on the clinical scenario and the preferences of the treating physician. Given the lack of specific diagnostic markers and the limitations of existing diagnostic criteria, clinical judgment plays a crucial role in the diagnosis of AOSD. A thorough history and physical examination, along with a comprehensive review of laboratory and imaging findings, are essential to evaluate the possibility of AOSD and exclude other potential diagnoses. A detailed history, including the patient's symptoms, past medical history, family history, and social history, can provide valuable clues for the diagnosis of AOSD. A thorough physical examination, including assessment of the skin, joints, lymph nodes, and other organ systems, is also essential. Laboratory investigations, including complete blood count (CBC), ESR, CRP, ferritin, liver function tests, and autoimmune markers, can help support the diagnosis of AOSD and exclude other conditions. Imaging studies, such as chest X-ray, CT scan, and MRI, can also be helpful in excluding other diagnoses or assessing for complications of AOSD. A multidisciplinary approach involving rheumatologists, internists, infectious disease specialists, and other specialists may be necessary to arrive at a definitive diagnosis of AOSD. This collaborative approach can help ensure that all potential diagnoses are considered and that the patient receives the most appropriate care. In some cases, a diagnostic trial of corticosteroids may be considered if the clinical suspicion for AOSD is high despite inconclusive diagnostic findings. A dramatic response to corticosteroids can further support the diagnosis of AOSD. In the presented case, the patient's past medical history of rheumatic fever initially raised the possibility of a recurrence or a related condition. However, the absence of cardiac involvement and the presence of characteristic AOSD features, such as the salmon-pink rash and markedly elevated ferritin levels, helped differentiate AOSD from other potential diagnoses. The development of hypercoagulability and ocular vasculitis further complicated the diagnostic process. These complications are rare in AOSD and can mimic other conditions, such as thrombotic thrombocytopenic purpura (TTP) or systemic vasculitis. However, the patient's overall clinical picture, including the characteristic AOSD features and the response to treatment, supported the diagnosis of AOSD with complications.[11,12]

Hypercoagulability, a condition characterized by an increased propensity for blood clot formation, is a rare but serious complication of adult-onset Still's disease (AOSD). This prothrombotic state can lead to life-threatening thromboembolic events, including deep vein thrombosis (DVT), pulmonary embolism (PE), and stroke. While the exact mechanisms underlying hypercoagulability in AOSD remain incompletely understood, it is believed to be intricately linked to the systemic inflammation and subsequent activation of the coagulation cascade that characterize this autoinflammatory disorder. AOSD is characterized by a dysregulated inflammatory response, with elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). These cytokines play a pivotal role in driving the systemic inflammation seen in AOSD, but they also exert significant effects on the coagulation system. IL-6, in particular, has been implicated in the pathogenesis of hypercoagulability in AOSD. This cytokine stimulates the production of fibrinogen, a key protein involved in blood clot formation, and promotes the expression of tissue factor (TF), a potent initiator of the coagulation cascade. TF, normally expressed by subendothelial cells and not in direct contact with circulating blood, becomes exposed to the bloodstream following vascular injury. In AOSD, however, the inflammatory milieu can induce TF expression on monocytes and endothelial cells, even in the absence of overt vascular damage. This aberrant TF expression can trigger the coagulation cascade, leading to thrombin generation and fibrin formation, ultimately culminating in blood clot formation. TNF-α, another key cytokine implicated

in AOSD pathogenesis, also contributes to the hypercoagulable state. TNF-α promotes platelet activation and aggregation, further enhancing the prothrombotic environment. Additionally, TNF-α can induce endothelial dysfunction, impairing the natural anticoagulant mechanisms that normally prevent excessive clot formation. In addition to IL-6 and TNF-α, interleukin-1 (IL-1) has also been implicated in the hypercoagulable state associated with AOSD. IL-1 is a potent pro-inflammatory cytokine that plays a key role in the pathogenesis of AOSD. Studies have shown that IL-1 can induce the expression of TF on monocytes and endothelial cells, thereby promoting coagulation activation. Furthermore, IL-1 can stimulate the production of other procoagulant factors, such as von Willebrand factor (vWF) and plasminogen activator inhibitor-1 (PAI-1). Endothelial dysfunction, characterized by impaired function of the endothelial cells lining blood vessels, is another important contributor to hypercoagulability in AOSD. The endothelium plays a critical role in maintaining vascular homeostasis by regulating coagulation, fibrinolysis, and platelet function. In AOSD, the chronic inflammatory state can lead to endothelial dysfunction, promoting a prothrombotic environment. Endothelial dysfunction in AOSD can manifest as increased expression of adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), which promote leukocyte adhesion and activation. Activated leukocytes can release various pro-inflammatory mediators, further amplifying the inflammatory response and contributing to hypercoagulability. Oxidative stress, an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defenses, has also been implicated in the pathogenesis of hypercoagulability in AOSD. ROS can damage endothelial cells, impairing their function and promoting a prothrombotic state. Additionally, ROS can activate platelets and promote the release of procoagulant factors. The hypercoagulable state in AOSD is reflected in various laboratory markers, including elevated levels of fibrinogen and D-dimer. Fibrinogen, as mentioned earlier, is a key clotting factor, and its increased levels indicate an activated coagulation system. D-dimer, a degradation product of fibrin, is a marker of both coagulation and fibrinolysis. Elevated D-dimer levels suggest ongoing clot formation and breakdown, further supporting the presence of a hypercoagulable state. In the presented case, the patient exhibited elevated levels of both fibrinogen and D-dimer, confirming the presence of hypercoagulability. These findings, along with the clinical presentation of hematomas, underscore the importance of recognizing and managing this potentially life-threatening complication in AOSD. In addition to fibrinogen and D-dimer, other markers of hypercoagulability that may be elevated in AOSD include prothrombin fragment 1+2 (F1+2), thrombin-antithrombin complex (TAT), and soluble P-selectin. These markers reflect different aspects of the coagulation cascade and can provide a more comprehensive assessment of the hypercoagulable state. While laboratory markers can be helpful in identifying patients with hypercoagulability, they have limitations. These markers are not specific to AOSD and can be elevated in various other conditions, including infections, malignancies, and other autoimmune diseases. Furthermore, the absence of elevated markers does not necessarily rule out hypercoagulability, as some patients may have a subclinical prothrombotic state. The hypercoagulable state in AOSD can manifest as various thromboembolic events, ranging from relatively minor events, such as superficial thrombophlebitis, to life-threatening complications, such as DVT, PE, and stroke. DVT, the formation of a blood clot in a deep vein, typically in the legs, can cause leg pain, swelling, and redness. However, DVT can also be asymptomatic and may only become apparent when a portion of the clot breaks off and travels to the lungs, causing a PE. PE, the lodging of a blood clot in the pulmonary arteries, can cause chest pain, shortness of breath, and even sudden death. Stroke, caused by a blood clot blocking an artery in the brain, can lead to various neurological deficits,

depending on the location and extent of the blockage. The risk of thromboembolic events in AOSD is influenced by various factors, including the severity of the underlying inflammation, the presence of other prothrombotic risk factors, and the use of certain medications, such as corticosteroids. VTE, encompassing both DVT and PE, is the most common thromboembolic complication in AOSD. Studies have reported a VTE incidence rate of 1-10% in AOSD patients. The risk of VTE is higher in patients with severe disease activity, those with a history of VTE, and those receiving corticosteroids. Arterial thromboembolism, including stroke and myocardial infarction, is less common than VTE in AOSD. However, it can be equally devastating. The risk of arterial thromboembolism is higher in patients with traditional cardiovascular risk factors, such as hypertension, hyperlipidemia, and smoking. Microvascular thrombosis, the formation of blood clots in small blood vessels, can also occur in AOSD. This can lead to organ damage, particularly in the kidneys, lungs, and central nervous system. The management of hypercoagulability in AOSD focuses on mitigating the risk of thromboembolic events. This typically involves anticoagulation therapy, using medications that prevent blood clot formation. The choice of anticoagulant depends on various factors, including the patient's individual risk factors, the severity of the hypercoagulable state, and the presence of any contraindications to specific anticoagulants. Commonly used anticoagulants in AOSD include low molecular weight heparin (LMWH), such as enoxaparin, and vitamin K antagonists (VKAs), such as warfarin. LMWH is often preferred for initial treatment due to its ease of administration and predictable anticoagulant effect. VKAs require regular monitoring to ensure therapeutic levels are maintained. In addition to anticoagulation, addressing the underlying inflammation in AOSD is crucial for managing hypercoagulability. Systemic corticosteroids, the mainstay of AOSD treatment, can help control inflammation and reduce the risk of thromboembolic events. DMARDs, such as methotrexate, may also be used to maintain remission and reduce the need for long-term corticosteroids. In some cases, prophylactic anticoagulation may be considered in AOSD patients who are at high risk of thromboembolic events, even in the absence of overt hypercoagulability. This may include patients with severe disease activity, those with a history of VTE, and those receiving high-dose corticosteroids. Patients with hypercoagulability in AOSD require close monitoring and follow-up to assess the efficacy of treatment and to detect any potential complications. This may involve regular blood tests to monitor coagulation parameters, as well as imaging studies to assess for thromboembolic events. In addition to medical management, lifestyle modifications can also play a role in managing hypercoagulability in AOSD. These may include maintaining a healthy weight, exercising regularly, and avoiding smoking.[13-15]

Ocular involvement in AOSD, while relatively uncommon, can lead to significant morbidity and potentially irreversible vision loss if not promptly diagnosed and managed. The most prevalent ocular manifestation is anterior uveitis, characterized by inflammation of the iris and ciliary body. This condition can cause pain, redness, photophobia, and blurred vision, significantly impacting a patient's quality of life. Other ocular manifestations associated with AOSD include keratitis (inflammation of the cornea), episcleritis (inflammation of the episclera), scleritis (inflammation of the sclera), and retinal vasculitis (inflammation of the retinal blood vessels). In this case report, the patient presented with both anterior uveitis and retinal vasculitis, highlighting the potential for severe ocular involvement in AOSD. The pathogenesis of ocular involvement in AOSD is complex and not fully elucidated, but it is believed to be closely related to the systemic inflammation that characterizes the disease. The dysregulated immune response in AOSD leads to the release of various pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-α, which can infiltrate ocular tissues and trigger inflammation. These cytokines can disrupt the blood-ocular barrier, allowing immune cells and

inflammatory mediators to enter the eye and cause damage to ocular structures. The specific mechanisms by which these inflammatory mediators cause ocular damage are still under investigation. However, it is believed that they can induce oxidative stress, activate complement pathways, and promote leukocyte adhesion and migration, all of which can contribute to ocular inflammation and tissue damage. While multiple cytokines contribute to the inflammatory milieu in AOSD, certain cytokines appear to play particularly prominent roles in driving ocular inflammation. IL-17, a pro-inflammatory cytokine produced by Th17 cells, has been implicated in the pathogenesis of uveitis in various autoimmune diseases, including AOSD. Studies have shown that IL-17 can induce the production of other pro-inflammatory cytokines and chemokines in the eye, leading to leukocyte infiltration and tissue damage. Another cytokine, interferon-gamma (IFN-γ), has also been implicated in ocular inflammation in AOSD. IFN-γ is a potent activator of macrophages, which can release various inflammatory mediators and contribute to tissue damage. Elevated levels of IFN-γ have been found in the aqueous humor of patients with AOSD-associated uveitis, suggesting a direct role for this cytokine in ocular inflammation. Genetic factors may also contribute to the susceptibility to ocular involvement in AOSD. Certain HLA genes, particularly HLA-B27, have been associated with an increased risk of uveitis in various autoimmune diseases, including AOSD. While the exact mechanisms by which HLA genes contribute to ocular inflammation are not fully understood, it is believed that they may influence the immune response to certain antigens or pathogens, leading to a dysregulated inflammatory response in the eye. Environmental triggers, such as infections or certain medications, may also play a role in triggering or exacerbating ocular inflammation in AOSD. For example, viral infections, such as herpes simplex virus (HSV) or cytomegalovirus (CMV), have been associated with uveitis in some AOSD patients. Certain medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), have also been reported to trigger or worsen uveitis in some individuals. The ocular manifestations of AOSD can vary widely in severity and presentation. Anterior uveitis, the most common manifestation, can range from mild and self-limiting to severe and chronic, potentially leading to complications such as glaucoma, cataract, and macular edema. Keratitis, inflammation of the cornea, can cause pain, photophobia, and decreased vision. Episcleritis and scleritis, inflammation of the episclera and sclera, respectively, can cause redness, pain, and tenderness of the affected eye. Retinal vasculitis, inflammation of the retinal blood vessels, can lead to vision loss if not promptly treated. In rare cases, AOSD can also cause panuveitis, inflammation of all layers of the uvea, or even optic neuritis, inflammation of the optic nerve. Anterior uveitis is the most common ocular manifestation of AOSD, occurring in approximately 20-40% of patients. It is characterized by inflammation of the iris and ciliary body, the structures responsible for controlling the amount of light entering the eye and focusing the lens. Anterior uveitis in AOSD typically presents with pain, redness, photophobia, and blurred vision. On examination, the affected eye may show signs of ciliary injection (redness around the cornea), cells and flare in the anterior chamber (indicating inflammation), and keratic precipitates (white blood cell deposits on the back of the cornea). Posterior uveitis, inflammation of the choroid and retina, is less common than anterior uveitis in AOSD, occurring in approximately 5-10% of patients. It can cause blurred vision, floaters (dark spots in the visual field), and decreased visual acuity. On examination, posterior uveitis may show signs of vitritis (inflammation of the vitreous humor), retinal infiltrates, and vasculitis. In severe cases, posterior uveitis can lead to retinal detachment and vision loss. Other ocular manifestations associated with AOSD include keratitis, episcleritis, scleritis, and optic neuritis. These manifestations are less common than anterior and posterior uveitis, but they can still cause significant morbidity and require prompt treatment to prevent vision loss. Diagnosing ocular involvement in

AOSD can be challenging, as the ocular manifestations can mimic other ocular conditions, such as infectious uveitis or other autoimmune uveitis. A thorough ophthalmological examination, including slit-lamp examination and funduscopy, is crucial to assess the extent of ocular involvement and identify any specific features suggestive of AOSD. In some cases, additional diagnostic tests, such as fluorescein angiography or optical coherence tomography (OCT), may be necessary to evaluate the retinal vasculature and assess for macular edema or other complications. Differentiating AOSD-associated uveitis from other forms of uveitis can be challenging, as there are no pathognomonic features specific to AOSD. However, certain clinical clues may suggest AOSD-associated uveitis, such as the presence of systemic features of AOSD, such as fever, rash, and arthritis. Laboratory findings, such as elevated inflammatory markers and hyperferritinemia, can also support the diagnosis of AOSD-associated uveitis. However, these findings are not specific to AOSD and can be seen in other inflammatory conditions. A multidisciplinary approach involving rheumatologists and ophthalmologists is often necessary to diagnose and manage ocular AOSD. Rheumatologists can provide expertise in the diagnosis and management of AOSD, while ophthalmologists can provide specialized care for the ocular manifestations. The treatment of ocular AOSD aims to control inflammation and prevent vision loss. Topical corticosteroids, such as prednisolone acetate eye drops, are often the first-line treatment for anterior uveitis. In more severe cases, systemic corticosteroids or immunomodulatory agents, such as methotrexate or biologics, may be necessary. Cycloplegic agents, such as cyclopentolate or atropine, are often used to dilate the pupil and relieve pain associated with anterior uveitis. In cases of retinal vasculitis, systemic corticosteroids or immunomodulatory agents may be required to control inflammation and prevent vision loss. Regular ophthalmological follow-up is essential to monitor the response to treatment and detect any potential complications. Patients with ocular AOSD should be educated about the importance of adherence to treatment and regular eye examinations to prevent vision loss. Topical corticosteroids are the mainstay of treatment for anterior uveitis in AOSD. They work by suppressing inflammation in the eye and reducing the associated symptoms, such as pain, redness, and photophobia. The choice of topical corticosteroid and the frequency of administration depend on the severity of the uveitis. In mild cases, a low-potency corticosteroid, such as prednisolone acetate 1%, may be sufficient. In more severe cases, a higher-potency corticosteroid, such as dexamethasone 0.1%, may be necessary. Systemic corticosteroids, such as prednisone or methylprednisolone, may be necessary in cases of severe or refractory uveitis, or when there is evidence of systemic involvement. Systemic corticosteroids are more potent than topical corticosteroids and can effectively suppress inflammation throughout the body. However, systemic corticosteroids can have significant side effects, such as weight gain, osteoporosis, and increased risk of infections. Therefore, they are typically reserved for cases where topical corticosteroids are insufficient or when there is a risk of vision loss. Immunomodulatory agents, such as methotrexate, azathioprine, and biologics, may be used in conjunction with corticosteroids to control inflammation and reduce the need for long-term corticosteroid use. These agents work by suppressing the immune system and reducing the production of inflammatory mediators. Methotrexate is a commonly used DMARD that can be effective in controlling ocular inflammation in AOSD. Biologics, such as TNF-α inhibitors (e.g., infliximab, adalimumab) and IL-6 inhibitors (e.g., tocilizumab), have also shown promising results in the treatment of ocular AOSD. Cycloplegic agents, such as cyclopentolate or atropine, are often used to dilate the pupil and relieve pain associated with anterior uveitis. Dilation of the pupil helps to prevent synechiae formation, which is the adhesion of the iris to the lens, and can also reduce pain by relaxing the ciliary muscle. The prognosis of ocular AOSD varies depending on the severity of the ocular involvement

and the response to treatment. Most patients with anterior uveitis respond well to topical corticosteroids and have a good visual prognosis. However, patients with more severe ocular involvement, such as retinal vasculitis or panuveitis, may have a worse prognosis and require more aggressive treatment to prevent vision loss. Several factors can affect the prognosis of ocular AOSD, including the severity of the initial presentation, the presence of complications, and the response to treatment. Patients with early diagnosis and prompt treatment generally have a better prognosis than those with delayed diagnosis or inadequate treatment.[16-18]

The management of AOSD with complications such as hypercoagulability and ocular vasculitis necessitates a multifaceted and individualized approach, often involving a multidisciplinary team of specialists, including rheumatologists, ophthalmologists, and hematologists. The primary goals of treatment are to control systemic inflammation, prevent and manage thromboembolic events, address ocular manifestations, and improve the patient's overall quality of life. Systemic corticosteroids remain the cornerstone of AOSD treatment, particularly in the acute phase of the disease. These potent anti-inflammatory agents effectively suppress the immune response, reducing the production of pro-inflammatory cytokines that drive the systemic inflammation and contribute to complications such as hypercoagulability and ocular vasculitis. In the presented case, the patient received intravenous methylprednisolone initially to rapidly control the severe systemic inflammation. Once his condition stabilized, he was transitioned to oral prednisolone, with a gradual tapering of the dose as his symptoms improved. While systemic corticosteroids are highly effective in the short term, their long-term use is associated with significant side effects, including weight gain, osteoporosis, increased risk of infections, and metabolic disturbances. Therefore, the goal is to use the lowest effective dose for the shortest duration possible, often in conjunction with other medications to achieve and maintain remission. DMARDs, such as methotrexate, are often added to the treatment regimen to reduce the reliance on corticosteroids and maintain long-term remission. These medications work by modulating the immune response and suppressing inflammation, although their exact mechanisms of action in AOSD are not fully understood. Methotrexate, a commonly used DMARD in AOSD, has been shown to be effective in controlling disease activity and reducing the frequency of flares. It is often used in combination with corticosteroids, allowing for lower corticosteroid doses and minimizing the risk of side effects. Other DMARDs, such as azathioprine, leflunomide, and cyclosporine, may also be considered in AOSD, although their efficacy and safety profiles have not been as extensively studied as methotrexate. In cases of refractory AOSD or when conventional DMARDs are ineffective or poorly tolerated, biologic agents may be considered. These targeted therapies specifically inhibit key molecules involved in the inflammatory cascade, such as TNF-α, IL-1, or IL-6. TNF-α inhibitors, such as infliximab and adalimumab, have shown promising results in the treatment of AOSD, particularly in patients with severe or refractory disease. IL-1 inhibitors, such as anakinra and canakinumab, and IL-6 inhibitors, such as tocilizumab, have also shown efficacy in AOSD. The choice of biologic agent depends on various factors, including the patient's specific clinical manifestations, disease severity, and comorbidities. Biologic agents are generally well-tolerated, but they can be associated with an increased risk of infections and other side effects. Anticoagulation therapy is crucial in AOSD patients with hypercoagulability to prevent potentially life-threatening thromboembolic events. The choice of anticoagulant depends on various factors, including the severity of hypercoagulability, the risk of bleeding, and the patient's preferences. In the presented case, the patient initially received enoxaparin, a low molecular weight heparin (LMWH), due to its rapid onset of action and predictable anticoagulant effect. Once his condition stabilized, he was transitioned to warfarin, a vitamin K antagonist (VKA), for long-term anticoagulation. Warfarin

requires regular monitoring of the international normalized ratio (INR) to ensure therapeutic levels are maintained. The target INR range for AOSD patients with hypercoagulability is typically between 2.0 and 3.0. Other anticoagulants, such as direct oral anticoagulants (DOACs), may also be considered in AOSD, although their efficacy and safety profiles in this specific population have not been extensively studied. The management of ocular vasculitis in AOSD aims to control inflammation and prevent vision loss. Topical corticosteroids, such as prednisolone acetate eye drops, are often the first-line treatment for anterior uveitis. In more severe cases, systemic corticosteroids or immunomodulatory agents may be necessary. Cycloplegic agents, such as cyclopentolate or atropine, are often used to dilate the pupil and relieve pain associated with anterior uveitis. In cases of retinal vasculitis, systemic corticosteroids or immunomodulatory agents may be required to control inflammation and prevent vision loss. Regular ophthalmological follow-up is essential to monitor the response to treatment and detect any potential complications. Patients with ocular AOSD should be educated about the importance of adherence to treatment and regular eye examinations to prevent vision loss. Patients with AOSD and complications such as hypercoagulability and ocular vasculitis require close monitoring and follow-up to assess the efficacy of treatment and detect any potential complications. Regular assessments should include monitoring of disease activity, laboratory parameters, and ocular manifestations. Disease activity can be assessed through clinical evaluation, including assessment of symptoms, physical examination findings, and laboratory markers such as ESR, CRP, and ferritin. Regular blood tests should also be performed to monitor for potential side effects of medications, such as liver function tests for methotrexate and complete blood counts for other DMARDs or biologics. Ophthalmological follow-up is essential to monitor the response of ocular manifestations to treatment and to detect any new or worsening ocular complications. The frequency of follow-up depends on the severity of the ocular involvement and the stability of the disease. Patient education and support are crucial components of AOSD management, particularly in patients with complications. Patients should be educated about their disease, its potential complications, and the importance of adherence to treatment. They should also be encouraged to adopt a healthy lifestyle, including regular exercise, a balanced diet, and stress management techniques, to promote overall well-being. Support groups and online resources can provide valuable information and emotional support for AOSD patients and their families. Healthcare providers should encourage patients to utilize these resources and to actively participate in their own care.[19,20]

4. Conclusion

This case report underscores the rare and serious complications of adult-onset Still's disease (AOSD), emphasizing the importance of early recognition and prompt treatment to prevent morbidity and mortality. The patient's presentation with hypercoagulability and ocular vasculitis highlights the diverse manifestations of AOSD and the potential for multi-organ involvement. The successful management of this case with a combination of systemic corticosteroids, DMARDs, and anticoagulation therapy demonstrates the importance of a multidisciplinary approach in managing AOSD and its complications. Hypercoagulability in AOSD, while rare, can lead to life-threatening thromboembolic events. The exact mechanisms underlying hypercoagulability in AOSD are not fully understood but are thought to be related to systemic inflammation and activation of the coagulation cascade. Elevated levels of fibrinogen and D-dimer, as seen in this case, are indicative of a hypercoagulable state and underscore the importance of anticoagulation therapy in managing this complication. Ocular involvement in AOSD, although uncommon, can lead to significant morbidity and potentially irreversible vision loss if left untreated. The most common ocular manifestation is anterior uveitis,

but other manifestations, such as retinal vasculitis, as seen in this case, can also occur. The pathogenesis of ocular involvement in AOSD is complex and likely involves a combination of immune dysregulation, genetic factors, and environmental triggers. This case report emphasizes the need for a high index of suspicion for AOSD in patients presenting with fever, rash, and arthritis, even in the absence of classic features. Early diagnosis and prompt treatment are essential to prevent complications and improve patient outcomes. Further research is needed to better understand the pathogenesis of AOSD and its complications, and to develop more targeted and effective therapies.

5. References

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