

CASE REPORT

Venous Thromboembolism Secondary to Adult-Onset Still's Disease: a Case Report

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ABSTRACT

A 56-year-old man presented to the emergency department with pain, swelling, and restricted mobility of the left lower limb and shortness of breath on exertion in the previous 3 days. Seven months prior to this presentation, he had been diagnosed with adult-onset Still's disease based on the Yamaguchi criteria, after excluding the presence of any other disease. The patient had been treated with prednisolone and methotrexate. Subsequent investigations revealed that he developed bilateral deep venous thrombosis and bilateral pulmonary emboli. This case emphasizes that adult-onset Still's disease can be a rare but life-threatening cause of venous thromboembolism.

Keywords: adult-onset Still's disease, deep venous thrombosis, pulmonary emboli

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INTRODUCTION

Adult-onset Still's disease (AOSD) is considered a complex autoinflammatory syndrome of unknown cause.¹ AOSD is a rare multisystemic disease, with an estimated prevalence of under 1 case per 100,000 subjects.²

This syndrome was described in 1897 by George Frederic Still as a chronic joint disease which appears in childhood.³ After 70 years, in 1967, the existence of the adult form of the syndrome was acknowledged.⁴ The clinical picture in an AOSD patient is characterized by fever (above 39°C), arthralgia, sore throat, and rash.⁵ Other features, representative for this rare condition, are lymphadenopathy, hepatosplenomegaly, pleurisy, pericarditis, and involvement of the central nervous system.^{6,7} The diagnosis of

AOSD is currently established based on Yamaguchi's criteria (Table 1), according to which the diagnosis requires the presence of at least five criteria, out of which at least two major.⁸

Pulmonary embolism (PE) is a major cardiovascular emergency, associated with a mortality rate of approximately 30%.⁹ Nowadays, anticoagulant therapy is considered the mainstay of medical therapy, decreasing the mortality associated to this major emergency to 2–8%.¹⁰ Therefore, a quick and accurate diagnosis of this condition could be vital to allow the prompt initiation of effective therapy.¹¹

In this case report we aim to demonstrate how deep vein thrombosis (DVT) and a consequent PE can represent a potential complication of AOSD.

TABLE 1. Diagnostic criteria for adult-onset Still's disease⁷

MAJOR CRITERIA	MINOR CRITERIA	EXCLUSION CRITERIA
Fever >39°C, lasting 1 week or longer	Sore throat	Infections
Arthralgia or arthritis, lasting 2 weeks or longer	Recent development of significant lymphadenopathy	Malignancies (malignant lymphoma)
Typical salmon-colored rash	Hepatomegaly or splenomegaly	Other rheumatic disease (systemic vasculitides)
Leukocytosis >10,000/mm ³ with >80 polymorphonuclear cells	Abnormal liver function tests	
	Negative tests for antinuclear antibody (IF) and rheumatoid factor (IgM)	

CASE PRESENTATION

We report the case of a 56-year-old Caucasian man who was referred to the hospital after presenting with pain, edema, and restricted mobility of the left lower limb and shortness of breath on exertion in the last 3 days. The initial examination of the patient revealed a mildly elevated arterial pressure (142/88 mmHg) and a peripheral oxygen saturation of 97%. Physical examination showed the presence of painful edema of the left leg. Laboratory tests revealed a hemoglobin level of 11.9 g/dL, elevated levels of C-reactive protein (19.7 mg/L), leukocytosis (15,585/ μ L), a ferritin level of 435.9 ng/mL, an erythrocyte sedimentation rate of 37 mm/1st h, and a D-Dimer concentration of >5 μ g/mL. Abdominal examination showed mild hepatosplenomegaly. Transthoracic echocardiogram revealed mild mitral and aortic valve regurgitation, without any vegetations or pericardial effusion.

Deep vein thrombosis (DVT) was suspected based on the patient's symptoms and elevated levels of D-dimers.

Venous Doppler ultrasound of the lower limbs discovered extensive bilateral DVT, with an occlusive thrombus in the right common femoral vein, right popliteal and calf veins, associated with occlusive thrombosis in the left common femoral vein, left femoral vein, left popliteal and left calf veins, and lymph nodes up to 17/7 mm in size in the right inguinal area (Figures 1–3).

Computed tomography (CT) scanning with intravenous contrast showed bilateral pulmonary emboli, larger in the right pulmonary artery, extending to the level of the upper and lower branches and emboli in the inferior branch of the right pulmonary artery (Figure 4).

The patient was diagnosed with AOSD 7 months prior and was initially under treatment with non-steroidal anti-inflammatory drugs (NSAIDs). Because his symptomatology did not respond to NSAIDs, he received prednisolone and methotrexate. At the time of the AOSD diagnosis, our patient fulfilled 2 major and 4 minor criteria of diagnosis

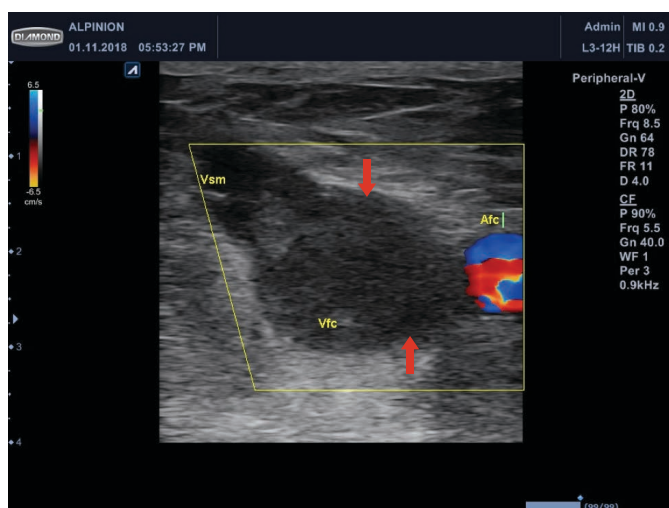


FIGURE 1. Venous Doppler ultrasound revealed a bulky intraluminal, partially occlusive thrombus in the right common femoral vein (arrow)

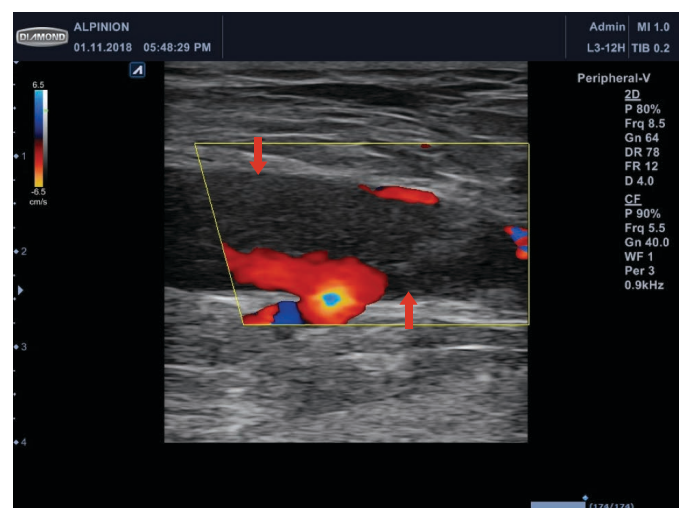


FIGURE 2. Venous Doppler ultrasound revealing intraluminal thrombus with marginal flow (arrow)

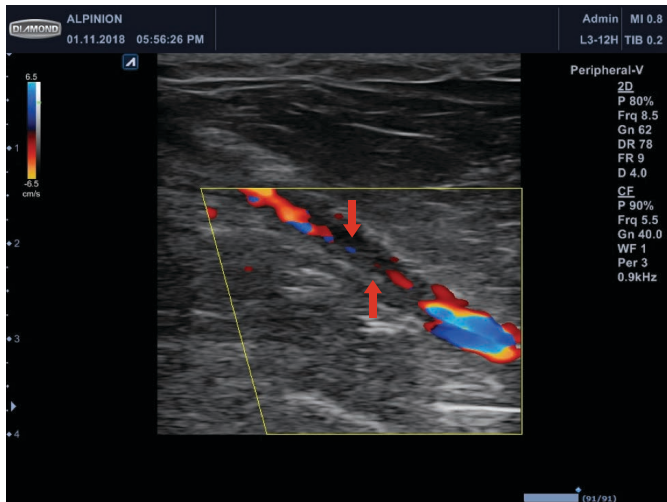


FIGURE 3. Venous Doppler ultrasound revealing a partially occlusive thrombus with marginal flow (arrow)

according to Yamaguchi's list (Table 2). At presentation, the patient was under treatment with prednisolone and methotrexate, and the symptomatology of AOSD was partially improved.

In order to improve survival and to prevent complications, the patient was instructed to wear venous compression stockings and anticoagulant therapy was initiated with low-molecular weight heparin and oral rivaroxaban.

The evolution of the patient was favorable, and he was discharged after several days, with significant improve-

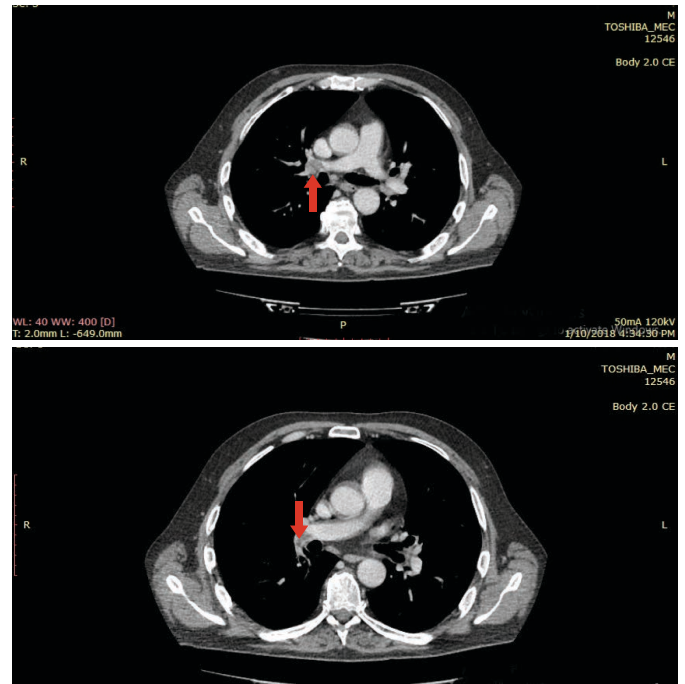


FIGURE 4. Computed tomography angiography revealing pulmonary arterial emboli in the right pulmonary artery (arrows)

ment of his clinical signs and symptoms, without developing any bleeding complications.

The presentation of this case was approved by the Ethics Committee of the hospital and written informed consent was obtained from the patient.

TABLE 2. Yamaguchi criteria in the patient with AOSD

	Present	Absent
MAJOR CRITERIA		
Fever >39°C, lasting 1 week or longer		X
Arthralgia or arthritis, lasting 2 weeks or longer	X	
Typical salmon-colored rash		X
Leukocytosis >10.000/mm ³ with >80 polymorphonuclear cells	X	
MINOR CRITERIA		
Sore throat		X
Recent development of significant lymphadenopathy	X	
Hepatomegaly or splenomegaly	X	
Abnormal liver function tests	X	
Negative tests for antinuclear antibody (IF) and rheumatoid factor (IgM)	X	
EXCLUSION CRITERIA		
Infections		X
Malignancies (malignant lymphoma)		X
Other rheumatic disease (systemic vasculitides)		X

DISCUSSIONS

Venous thromboembolism involves both deep vein thrombosis and pulmonary embolism and is an extremely serious condition, with an estimated occurrence of approximately 1 in 1,000 adults annually.¹² The potential risk factors for this devastating disease are numerous: malignancy, different types of trauma, protein C or S deficiency.¹³

Important epidemiologic data on AOSD are missing. AOSD affects predominantly young adults, although it can also be present among geriatric patients.^{14–17} Cagatay *et al.* demonstrated that women seem to be more affected than men by this rare disease.¹⁸ The mechanisms underlying AOSD are not fully known to date; however, different studies have been published suggesting a role of genetic, infectious and environmental factors in the physiopathology of this syndrome.¹⁹

The diagnosis of AOSD is based on Yamaguchi's criteria (1992), which were associated with a sensitivity of 93.5% for diagnosing this disease.²⁰ These criteria include 4 major criteria (fever above 39°C lasting one week or longer, arthralgia or arthritis lasting 2 weeks or longer, typical rash and leukocytosis above 10,000/mm³) and 5 minor criteria (sore throat, recent development of significant lymphadenopathy, hepatomegaly or splenomegaly, abnormal liver function tests, and negative tests for antinuclear antibody and rheumatoid factor).⁷ Our patient fulfilled 2 major and 4 minor criteria when he was first diagnosed with AOSD.

Other features representative for this disease are myalgia, lymphadenopathy, pleurisy, pericarditis, weight loss, and involvement of the central nervous system.⁶ In most cases of AOSD (more than 70% of the patients), laboratory findings show elevation of the erythrocyte sedimentation rate, leukocytosis, and elevated ferritin levels, as seen in our patient.^{18,21} However, other diagnoses such as rheumatic diseases (mainly systemic vasculitis), infections and malignancies (mainly malignant lymphoma) should be excluded before establishing the final diagnosis of AOSD.²⁰

Two distinct AOSD phenotypes can be differentiated in the general population: the first type is exceedingly symptomatic, characterized by fever, which could develop into a systemic pattern (mono- or polycyclic); the second type is characterized by arthritis as the main symptom and poor systemic symptomatology, developing a chronic articular pattern.^{22,23}

In clinical practice, it is very important to recognize the clinical and laboratory characteristics of AOSD, an uncommon disorder with multiple non-specific signs and symptoms, as it may generate different medical complications.

The association between AOSD and pulmonary embolism is rare, but several studies addressed this interesting correlation. In a retrospective study, Al-Temimi *et al.* collected data from 6 patients diagnosed with AOSD, highlighting the demographic and clinical features associated with this disease, and found that one of the 6 patients had a pulmonary embolism which led to death.²⁴ Also, a study by Merashli *et al.* identified venous thromboembolism as an initial manifestation of AOSD.²⁵

According to other cases from the literature, venous thromboembolism occurs extremely rarely in AOSD, and this is possible due to enhanced coagulation activation.²⁶ Coagulation activation in AOSD can induce disseminated intravascular coagulation with multi-organ failure and also digital autoamputation.²⁷ According to several authors, NSAIDs or prednisolone and methotrexate could be recommended for subjects not responding to NSAIDs.^{28,29}

CONCLUSIONS

AOSD has several manifestations which can limit life expectancy. Venous thromboembolism, as a presentation of AOSD, is exceedingly rare, but life-threatening.

In our opinion, a careful consideration of the association between AOSD and coagulation imbalance should be further investigated in order to prevent the risk of massive and fatal thrombotic events in patients with AOSD.

CONFLICT OF INTEREST

Nothing to declare.

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