Adult-onset Still's Disease with a Rare Life-Threatening Complication of Acute Pulmonary Embolism: A Case Report and Literature Review

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ABSTRACT:
Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory disorder with unknown etiology that most commonly affects young female adults. The characteristic signs and symptoms of AOSD are high-spiking fever, evanescence salmon-pink rash and arthritis. Atypical cutaneous manifestations of AOSD can present with persistent pruritic papules and plaques, flagellate erythema, linear plaques or vesicular eruptions. Two serious complications which can occur in patients with AOSD are reactive hemophagocytic syndrome and thrombotic thrombocytopenic purpura. Pulmonary embolism is one of the cardiovascular emergencies which are rarely reported as a complication of AOSD. Here in, we report the case of a 35-year-old Burmese woman presented with subacute intermittent high-grade fever with sore throat, polyarthritis, and persistent pruritic rashes with flagellate erythema for 3 weeks. She fulfilled the criteria for the diagnosis of AOSD. During the admission, she developed a sudden onset of dyspnea subsequent investigation revealed an intraluminal filling defect at the lateral and posterior right lower lobes that was most compatible with pulmonary embolism. She was treated with oral naproxen, prednisolone 30 mg/day (0.6 mg/kg/day), cyclosporin A 50 mg/day, topical betamethasone cream 0.1% for AOSD, and received enoxaparin 0.6 mg SC twice daily for 1 week, then oral warfarin 2 mg/day for pulmonary embolism. After 4 weeks of switching treatments, her clinical condition was partially improved.

Key words: Adult-onset Still's disease, Pulmonary embolism, Flagellate erythema, Reactive hemophagocytic syndrome, Thrombotic thrombocytopenic purpura

Introduction

Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory disorder with unknown etiology that most commonly affects young female adults[1,2,3]. The characteristic signs and symptoms of AOSD are high-spiking fever, evanescence salmon-pink rash, and arthritis[1,4]. Atypical cutaneous manifestations of AOSD can present with persistent pruritic papules and plaques, flagellate erythema, linear plaques triggered by local trauma (Koebner phenomenon), or vesicular eruption[1,5,6]. The most commonly used criteria for AOSD diagnosis are Yamaguchi's and Fautrel's criteria which the exclusion of the other causes of fever is required[5,6]. Two serious complications which can occur in patients with AOSD are reactive hemophagocytic syndrome (RHS) and thrombotic thrombocytopenic purpura[3,7]. Pulmonary embolism (PE) is one of the cardiovascular emergencies which are rarely reported as a complication of AOSD[8,9,10,11,12].

Here in, we report the case of the first diagnosed AOSD, who subsequently developed acute pulmonary embolism during hospital admission.

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Case

A 35-year-old Burmese woman presented to Rajavithi Hospital with an intermittent fever for three weeks. Her febrile condition was concomitantly found with sore throat and arthralgia. Her joint pain involved both elbows, wrists, hands, knees, and ankles. She also developed pruritic erythematous rashes on her neck, arms, trunk, and back. She denied any history of photosensitivity, malar rash, oral ulcer, weakness, or palpitation. No other constitutional symptoms such as anorexia, night sweat, or weight loss, were observed. She denied a history of abortion, stillbirth, or use of oral contraceptive pills. She had a regular menstrual period with normal bleeding volume. No family history of thromboembolic diseases was noted.

At the hospital, she was initially treated as septic arthritis with ceftriaxone 2 g once daily for 9 days, but her clinical condition did not improve. A dermatological consultation was done to evaluate the skin rashes with subacute fever. Physical examination revealed vital signs as follows: body temperature 39°C, blood pressure 125/86 mmHg, pulse rate 120 beats per minute, full 2+, and regular and respiratory rate 18 times per minute. She developed faint blanchable erythematous patches on face with ill-defined scaly erythematous patches on neck (Figure 1A) with multiple linear erythematous to hyperpigmented papules and plaques some arranged in flagellate appearance on upper extremities, trunk and back. (Figure 1B-D) No lymphadenopathy, hepatosplenomegaly, or abnormal cardiopulmonary system were noted.

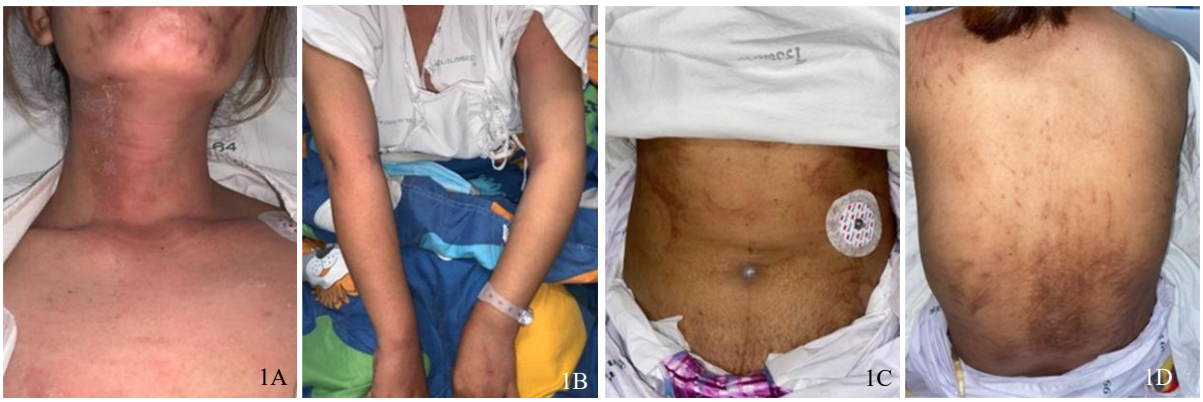

Figure 1 Faint blanchable erythematous patches on face with ill-defined scaly erythematous patches on neck (1A), multiple linear erythematous to hyperpigmented papules and plaques some arranged in flagellate appearance on upper extremities, trunk and back (1B-D)

Laboratory investigations showed a complete blood count as follows: white blood cells count 20,730/uL, neutrophils 92.3%, lymphocytes 6%, hemoglobin 10.1 g/dL, hematocrit 30.1%, platelets 294,000/uL, LDH 2,388 u/L (105 to 233 u/L), ferritin >167,556 (5-204 ng/mL), ESR 58 mm/hr (< 20 mm/hr), CRP 14.13 mg/dL (≤ 0.5 mg/dL), ASO titer 56.65 (0-200), serum triglycerides 318 mg/dL (< 150 mg/dL), elevation of AST 53 u/L and ALT 78 u/L. HBsAg, anti-HCV, and anti-HIV were negative. Other basic laboratory tests, including electrolytes, coagulograms, and renal function tests, were unremarkable. The septic workup revealed a negative blood culture and right knee arthrocentesis culture, but the cell count could not be evaluated due to fluid clots. Tropical disease infections, including chikungunya, leptospiral, and scrub typhus, were negative. Autoimmune antibodies showed an ANA 1:80 fine speckle pattern, rheumatoid factor <10 IU/mL, ANA 12 profiles, Anticardiolipin

antibody of IgG and IgM, and anti-β2 glycoprotein-I antibody of IgG and IgM were negative. Bone marrow aspiration and biopsy were insufficient. Investigations for hereditary thrombophilia, such as anticoagulant proteins, factor V leiden, protein C, and protein S, did not perform due to her financial problems, and she denied a history of abnormal clots.

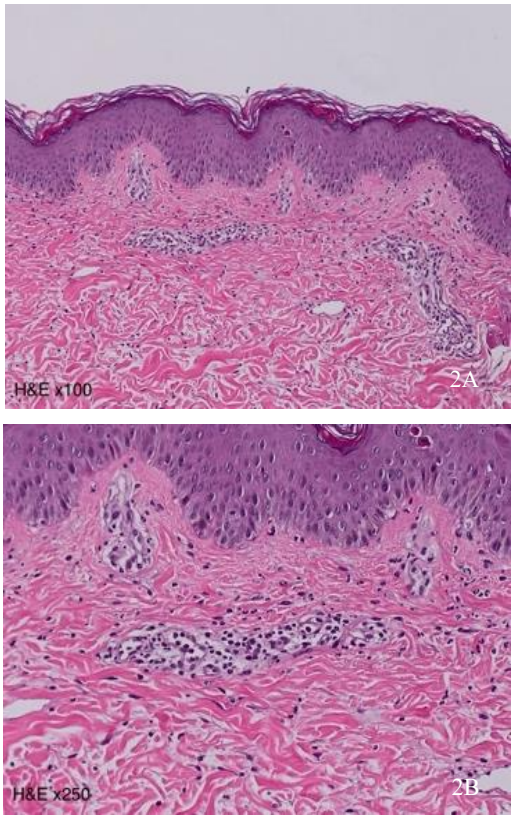

Figure 2A, 2B Sections displayed scattered necrotic keratinocytes in the upper epidermis. The dermis showed superficial and deep perivascular with interstitial inflammatory cell infiltrate of lymphocytes and numerous neutrophils

The punch biopsy was performed on her right elbow showed scattered necrotic keratinocytes in the upper epidermis. The dermis showed superficial and deep perivascular with interstitial inflammatory cell infiltrate of lymphocytes and numerous neutrophils. (Figure 2A-B)

This patient fulfilled the Yamaguchi criteria and histopathology was compatible with AOSD. She was treated with oral naproxen, prednisolone 30 mg/day (0.6 mg/kg/day), cyclosporin A 25 mg every 12 hours, and topical betamethasone cream 0.1%.

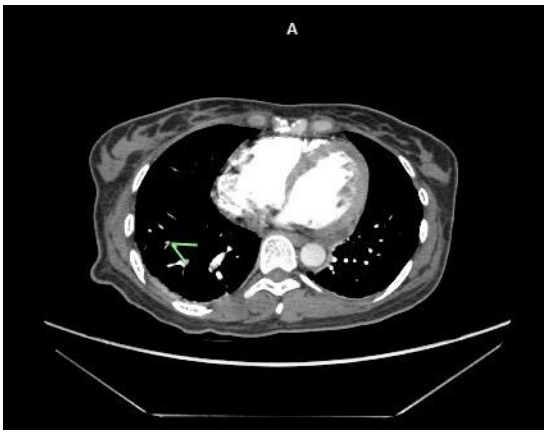

Figure 3 CT pulmonary angiogram (CTPA) displayed intraluminal filling defect at lateral and posterior right lower lung

Two weeks after the initial treatment, she developed a sudden onset of dyspnea, non-productive cough, and persistently high body temperature without chest discomfort, orthopnea, or paroxysmal nocturnal dyspnea. On physical examination, vital signs revealed persistent high-grade fever of 39.5°C, blood pressure 123/80 mmHg, pulse rate 128 beats per minute, tachypnea with respiratory rate of 24 times per minute, and decreased oxygen saturation room air at 93%. Her electrocardiogram showed sinus tachycardia rate 130 beat per minute. D-dimer >35.2 mg/L (0-0.5 mg/L), fibrinogen 323.3 mg/dL (200-400 mg/dL). Chest X-ray and coagulogram were unremarkable. CT pulmonary angiogram (CTPA) was done to evaluate the cause of dyspnea, and the result showed an intraluminal filling defect at lateral and posterior right lower

lung compatible with pulmonary embolism. (Figure 3)

She was diagnosed with AOSD and pulmonary embolism then was treated with anticoagulants, Enoxaparin 0.6 mg SC twice daily for 1 week then switched to warfarin 2 mg/day. Initially, her clinical status improved after all of these treatments. But after she was discharged from the hospital, unfortunately, she was lost to follow-up.

Discussion

Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory disorder that most commonly affects young female adults by a mean age of 36 years with a prevalence of 1.5 cases per 100,000–1,000,000 people[1,2,3]. The etiology of AOSD is unknown but many previous studies believe that the disorder might be caused by a combination of genetic factors, infections, or environmental exposures[3]. Additional proinflammatory cytokines as well as interleukin (IL)-1β, IL-2, IL-6, IL-18, TNF-α, and IFN-γ are elevated in patients with AOSD[3,4,5].

The characteristic signs and symptoms of AOSD are high-spiking fever, evanescence salmon-pink rash, and arthritis, as well as leukocytosis, high ferritinemia, and a negative antinuclear antibody test[1,4,5]. Atypical cutaneous manifestations of AOSD can present with persistent pruritic papules and plaques, flagellate erythema, linear plaques triggering by local trauma (Koebner phenomenon) were observed in 78% of AOSD[13] as seen in our patient or vesicular eruption[1,5,6]. These lesions may develop fine scale, and are the most commonly located on trunk, extremities, head, and neck. The color of atypical eruption was either erythematous or brown, and less commonly violaceous[1,14]. The most commonly used criteria for AOSD diagnosis is Yamaguchi's and Fautrel's criteria which the exclusion of the other causes of fever is required[5,6]. This patient fulfilled the Yamaguchi criteria, which included subacute intermittent high-grade fever with arthralgia, sore throat, leukocytosis, and liver enzyme abnormalities in the absence of infection, malignancy, or inflammatory disease.

Histopathology of the classic evanescent skin eruption is mild perivascular inflammation with neutrophils, intravascular neutrophils, and dermal edema. While atypical cutaneous lesions show a group of necrotic keratinocytes in upper dermis, sparse superficial dermal infiltration with neutrophils and sometimes eosinophils in the absence of vasculitis[1,2,5], these findings confirm our patient's diagnosis.

Most AOSD patients with atypical cutaneous lesions had persistent and severe disease causing significant clinical complications like serositis, myopericarditis, pleuritis, lung fibrosis, abdominal pain, neurologic involvement, and RHS[3,7,14,15]. As previously stated, two serious complications associated with AOSD are RHS and thrombotic thrombocytopenic purpura. An important newly recognized complication of AOSD is its association with malignancy including 50% hematopoietic malignancy (mostly lymphomas), and 50% solid tumors (breast, lung, esophagus, and liver angiosarcoma)[1,5]. Median time between diagnosis of AOSD and detection of malignancy was 9 months[5]. Overall, these serious complications must be excluded in our patient. She underwent bone marrow aspiration and biopsy but could not be evaluated due to insufficient bone marrow. Despite having extremely high ferritin levels, this patient did not meet the criteria for RHS diagnosis[7,13,16]. CTPA was performed due to progressive dyspnea; the images showed pulmonary embolism at the lateral and posterior right lower lobes.

According to the literature review (Table 1), there have been 5 cases reported of the association between AOSD and pulmonary embolism; 3 cases developed pulmonary embolism after admission with AOSD (ranging from 5 days to 7 months, similar to our patient),

and 2 cases of these were first hospitalized for pulmonary embolism before receiving an AOSD diagnosis for 2–10 days later. Pathogenesis probably explained by high ferritin levels enhanced inflammatory states and coagulation activation that developed fatal complications. These patients received the treatment as conventional AOSD with pulmonary embolism, similar to this report. According to documentation, 4 cases improved after receiving treatment, while 1 case died[8,9,10,11,12].

Table 1 Reported cases of association between AOSD and pulmonary embolism (PE)

No	Author	Country	Sex	Age (years)	Presentations	Treatment	Result
1	Mankgele M et al[8]. (2023)	South Africa	Female	43	- First diagnosed with AOSD - Developed PE 5 days after admission	- Prednisone - Methotrexate then switched to Cyclosporin - Enoxaparin then switched to Rivaroxaban	Improved
2	Al-Temimi FA et al[9]. (2006)	Oman	5 females (80.2%) 1 male (16.65%)	21.6 (by mean age)	- Fever (80.2%) - Skin rash (80.2%) - Arthralgia (100%) - Arthritis (66.65%)	-	1 patient died from PE
3	Bhamra M[10] (2018)	USA	Female	66	- Admitted due to PE - Diagnosed with AOSD 10 days after admission	- Prednisone - Methotrexate - Anticoagulant	Improved
4	Calborean V et al[11]. (2018)	Romania	Male	56	- Known case AOSD - Developed PE 7 months after treatment with AOSD	- Compression stockings - Enoxaparin then switched to Rivaroxaban - NSAIDs - Prednisolone - Methotrexate	Improved
5	Merashli M et al[12]. (2015)	London	Male	38	- Admitted due to PE - Diagnosed with AOSD 2-3 days after admission	- Prednisone - Methotrexate - Anticoagulant	Improved
6	Our case	Thailand	Female	35	- First diagnosed with AOSD - Developed PE 14 days after admission	- Prednisolone - Naproxen - Cyclosporin A - Enoxaparin then switched to warfarin	Lost followed up

Treatment of AOSD includes NSAIDs, glucocorticoids, steroid-sparing agents such as gold, D-penicillamine, sulfasalazine, hydroxychloroquine, methotrexate, thalidomide, azathioprine, cyclosporine, cyclophosphamide, and IV immunoglobulin to control arthritis and systemic disease[3,5]. Although NSAIDs are considered first-line therapy, their use in combination with glucocorticoids seems to be more effective in controlling disease[1,3]. The new biologic agents include anti-TNF agents, anakinra (anti–IL-1), rituximab, tocilizumab, and canakinumab (IL-6 receptor inhibitor) for resistant and chronic cases[1,3,5]. Our patient received oral naproxen, prednisolone 30 mg/day (0.6 mg/kg/day), cyclosporin A 50 mg/day, and topical betamethasone cream 0.1% for AOSD and received enoxaparin 0.6 mg SC twice daily for 1 week, then oral warfarin 2 mg/day for

pulmonary embolism. After 4 weeks of switching treatments, her clinical condition was partially improved.

But after she was discharged from the hospital, unfortunately, she was lost to follow-up.

Conclusion

AOSD can be present with atypical manifestations that can be easily misdiagnosed. Once diagnosed, searching for other serious complications is warranted. The life expectancy of patients with AOSD might be significantly decreased by systemic organ involvement. Acute pulmonary embolism is rare and can also be a fatal complication of AOSD.

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