Late Onset Evanescent Rash in a Patient with Adult-Onset Still's Disease

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ABSTRACT:

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Adult-onset Still's disease is a rare multisystem autoimmune disease characterized by fever, skin rash, arthritis, and hyperferritinemia. Skin rash usually develops along with the peak of fever. Specific diagnostic test has not been established yet. Therefore, the diagnosis is usually based on symptom complex and the skin rash. We present a case of adult-onset Still's disease in a healthy middle-aged man with prolonged fever for 4 month without any rash. The biopsy was taken from normal skin to exclude intravascular lymphoma. The evanescent rash developed 3 months after he had fever which raised physician about the diagnosis of adult-onset Still's disease. According to Yamaguchi criteria, the diagnosis criteria in this patient composed of fever, sore throat, rash, leukocytosis and transaminitis. Late manifestation of skin rash was underrecognized which leaded to delay diagnosis. The early recognition could be leaded to early diagnosis and appropriate treatment. This report demonstrates a late onset of cutaneous manifestation in patient with adult-onset Still's disease.

Key words: Adult onset Still's disease, cutaneous manifestation, late onset

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Introduction

Adult-onset Still's disease (AOSD) is a rare multisystem autoimmune disease consisted of fever, skin rash, arthritis, and hyperferritinemia, with bimodal distribution[1-9]. The typical cutaneous manifestation is evanescent maculopapular eruption but atypical cutaneous presentation has been also reported[1-5]. The skin rash usually come along with the fever and other systemic symptoms, but only little literature mentioned about the exact onset of cutaneous manifestations[1-9]. Late manifestation of skin rash was underrecognized which lead to delay diagnosis. The diagnosis of AOSD usually based on the Yamaguchi or Fautrel criteria after excluding infectious, malignant, and other autoimmune diseases[1-4,7]. Histologic findings in the evanescent rash of AOSD are broad and non-specific[5-6]. Conventional treatment for AOSD include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and steroid-sparing agents[3,4,7]. The use of biologic agents appear for an advance treatment in patients with refractory AOSD[3,4,7].

Case presentation

A 43-year-old man from Bangkok, presented with prolonged fever for 4 months. Initially he had upper respiratory tract symptoms. So, he was diagnosed with tonsillitis and received antibiotic therapies. He denied improvement of symptoms after received the therapies. Basic investigation revealed leukocytosis with neutrophilia and elevated liver enzymes. He had been under investigations for prolonged fever including hemoculture, hepatitis profile, anti-HIV, indirect immunofluorescent assay for systemic infection, computed tomography scan of chest and whole abdomen, and bone marrow biopsy and culture. All of the investigation results showed no evidence of infection or malignancy. After that, dermatologist was consulted for random normal skin biopsy to exclude intravascular lymphoma, because he had slightly elevated lactate dehydrogenase (LDH) level (363 U/L). The physical examination by dermatologist revealed no cutaneous eruption. The random biopsy was done at abdomen and right thigh. The histological examination showed perivascular lymphocytic infiltration without evidence of intravascular lymphoma (Figure 1).

After 4-month of prolong fever, he was admitted for intensive investigation of prolong fever. In the hospital, he had intermittent spiking fever at night and resolved in the morning. He also had sore throat. Physical examination showed neither hepatosplenomegaly nor lymphadenopathy. Erythematous maculopapular rash on trunk was initially developed during admission corresponding with high grade fever (Figure 2). The skin lesion spontaneously resolved without hyperpigmentation. Autoimmune profile showed positive antinuclear antibodies (ANA) at titer of 1:320 (fine speckle pattern) and borderline

level of rheumatoid factor (RF). Further specific autoantibody tests for systemic lupus erythematosus revealed negative. Considering the cutaneous eruption which corresponding to fever spikes, he was diagnosed as AOSD by using Yamaguchi criteria for AOSD which include fever, sore throat, typical skin rash, leukocytosis with neutrophil predominates, and abnormal liver enzymes after excluded infections, malignancies, and other connective tissue diseases. Prednisolone 30 mg/day and chloroquine 250 mg/day were given. His fever and symptoms were improved after treatment with low dose prednisolone. However, some maculopapular rash had not been completely disappeared. Therefore, methotrexate 10 mg/week was added to control the symptoms.

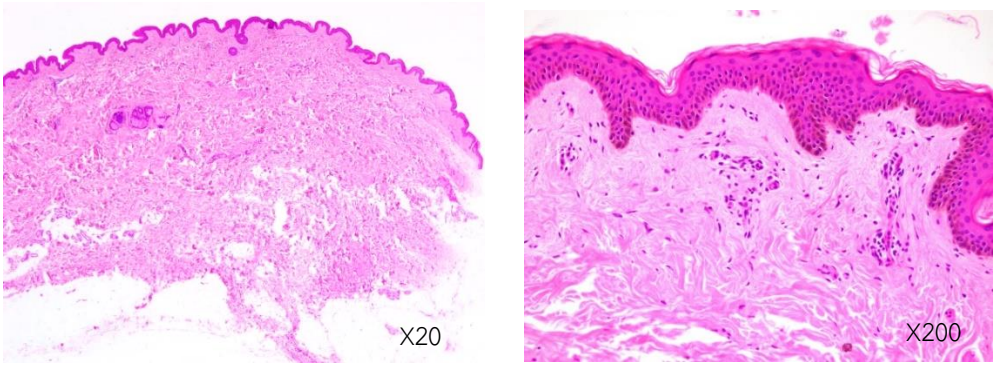

Figure 1 Incisional skin biopsy from right thigh revealed superficial perivascular infiltration by lymphocytes without vasculitis

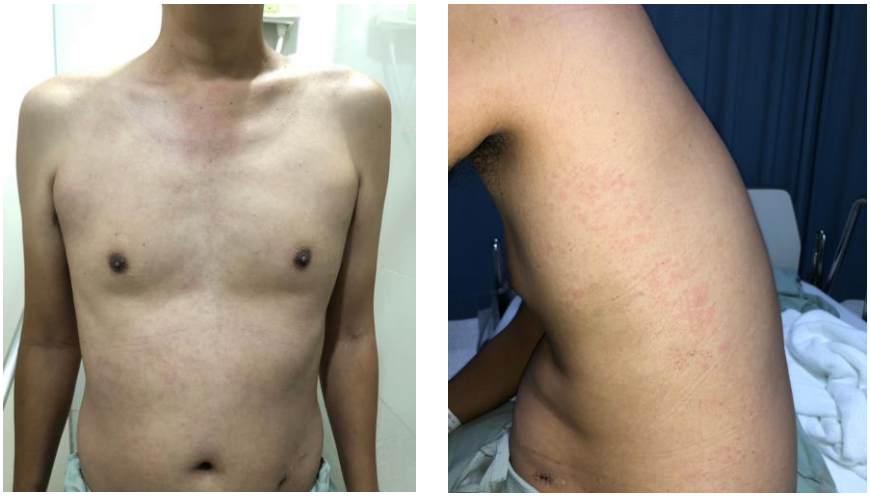

Figure 2 Multiple discrete blanchable erythematous macules and papules on trunk

Discussion

Cutaneous manifestations were found in 60-80% of AOSD patients[1-2]. The typical eruption consists of transient discrete, non-pruritic, salmon-pink maculopapules appearing along with fever spikes which compatible with this patient[1-3]. Atypical skin eruption was reported in some cases including persistent pruritic erythematous plaques, scaly plague, urticaria and lichenoid eruption[1-3]. He reported cutaneous manifestation 4 months after onset of fever that may considered late onset. Most of the patients show an evanescent rash concomitant with febrile attack[1-4], but only few literatures mentioned the exact onset of the cutaneous manifestation. One retrospective study in China showed skin rash being present from the initial onset of the disease in 27.87% of patient but didn't state the exact onset of cutaneous manifestations[10]. One case report of severe AOSD reported skin manifestation 20 days after initial fever[11]. Comparing to our patient, the duration between fever and rash development was longer than duration reported in previous report. Late onset of rash in patients with AOSD could be found therefore physicians should be aware of these conditions.

The histologic findings in the evanescent eruption are broad and non-specific, characterized by perivascular infiltration by lymphocytes or neutrophils with no evidence of vasculitis[1-6]. Interface changes were also documented[5-6]. Meanwhile, persistent papules and plaques of AOSD demonstrates different histologic findings which characterized by dyskeratosis in the epidermis with a perivascular infiltration without vasculitis[5-6]. Our patient skin biopsy specimens were taken from the normal-appearing skin sites which demonstrated superficial perivascular infiltration by lymphocytes without epidermal change or vasculitis. These findings can be found in AOSD but not specific to AOSD. Moreover, this case revealed that normal skin of patient with AOSD had pathological change. From literature review, report about histology from normal skin in patient with AOSD was limited. This may be the first description of a patient with a diagnosis of AOSD which demonstrated compatible histological findings from normal skin site.

The absence of antinuclear ANA and RF is one of minor criteria in Yamaguchi criteria[1-2,4,7]. This patient has positive ANA (fine speckled pattern at titer 1:320, nucleolar and cytoplasmic at titer 1:100) and borderline level of RF (16.94 IU/ml) without other evidence of lupus erythematosus. Minority of AOSD patients are positive for RF and/or ANA[4,7], so it is unreasonable to exclude AOSD if patients have positive titer of RF and/or ANA. Further study about the etiology and clinical course between positive and negative ANA in AOSD patients were required.

High serum ferritin was commonly reported in AOSD[1-4,7-8]. High serum ferritin produces high

sensitivity but no specificity. Intriguingly, serum ferritin which ≥1,000 ng/ml (5 times of upper normal limit), which is observed in this patient (16,055 ng/ml), provided sensitivity and specificity of 40.8% and 80% respectively[8]. Moreover, if high level of ferritin ≥1,000 ng/ml combines with serum glycosylated ferritin ≤20% can boost the sensitivity and specificity up to 70.5% and 92.9% respectively. Lately, it has been proposed that AOSD is one of "Hyperferritinemic syndrome" which characterized by very high serum ferritin level[4,8].

Nowadays, the treatments for AOSD are mainly symptomatic therapies[3-4]. Conventional treatments for AOSD include NSAIDs, corticosteroids, and steroid-sparing agents[3]. Recent studies showed that many cytokines including interleukin-1, 6, 8, and TNF-α take part in pathogenesis of AOSD. Biologic agents, which target mentioned cytokines, may be considered in refractory AOSD. This patient received oral prednisolone and chloroquine which can control his symptoms.

Conclusion

We report a case of late onset of classic cutaneous manifestation of AOSD. The rash developed after 4-month of fever. The abnormal histological findings could also be found in the normal skin of patient with AOSD. Maculopapular eruption which concomitant with fever was clinical clue for diagnosis.

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