



Atypical Still disease with necrotic keratinocytes: A histologic mimicker of erythema multiforme

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INTRODUCTION

Still disease, or systemic juvenile idiopathic arthritis (sJIA), and its adult form, adult-onset Still disease (AOSD), are illnesses characterized by daily fever, evanescent rash, and arthritis.¹ Typical rash is nonpruritic, salmon-pink, transient, and maculopapular. Typical histology shows dermal edema and perivascular neutrophils. Atypical Still disease is a variant characterized by persistent pruritic papules and plaques¹ with histologic necrotic keratinocytes.² We report 2 unique cases of atypical Still disease, one in an adult and the other in an adolescent.

CASE REPORT

Case 1

A 32-year-old woman presented with 2 weeks of fevers, intermittent rash, sore throat, and arthralgia. Zika infection was diagnosed 2 months prior, after she visited Ecuador.

Skin examination found scattered urticarial papules and plaques on her extremities and back and eczematous plaques with pinpoint necrosis on the neck and chest (Fig 1). The patient reported pruritus.

Bloodwork showed erythrocyte sedimentation rate of greater than 130 mm/h, C-reactive protein greater than 300 mg/L, mild transaminitis, white blood count of 18,100 cells/ μ L, ferritin level of 12,500 ng/mL, negative antinuclear antibody, rheumatoid factor (RF), and normal complement levels. Viral serology results were negative.

Diagnostic considerations included serum sickness, urticarial vasculitis, and AOSD. Dermatomyositis was considered given apparent shawl sign on the chest,

Abbreviations used:

ANA:	antinuclear antibody
AOSD:	adult-onset Still disease
RF:	rheumatoid factor
sJIA:	systemic juvenile idiopathic arthritis

although she lacked other dermatomyositis features and rheumatologic workup was unrevealing.

Skin biopsies from the right upper chest and thigh found a perivascular neutrophilic infiltrate and isolated necrotic keratinocytes in the upper layers of the epidermis (Fig 2). The patient ultimately was diagnosed with atypical AOSD and was treated with prednisone, 1 mg/kg/d, with resolution of cutaneous findings but persistent knee pain. She was subsequently lost to follow-up.

Case 2

A 13-year-old girl presented with 2 weeks of fevers, arthralgia, and intermittent urticarial eruption, which flared during febrile episodes. The rheumatology department suspected serum sickness related to a viral illness that occurred 1 month before the rash. Bloodwork showed white blood count of 14,000 cells/ μ L, erythrocyte sedimentation rate of 59 mm/h, C-reactive protein level of 182 mg/L, ferritin level of 24,712 ng/mL, positive ANA with 1:160 speckled/nucleolar pattern, normal RF, complement, anti-Smith antibody and antiribonucleoprotein antibody. Pharyngeal culture was negative. Symptoms improved with naproxen and hydroxyzine.

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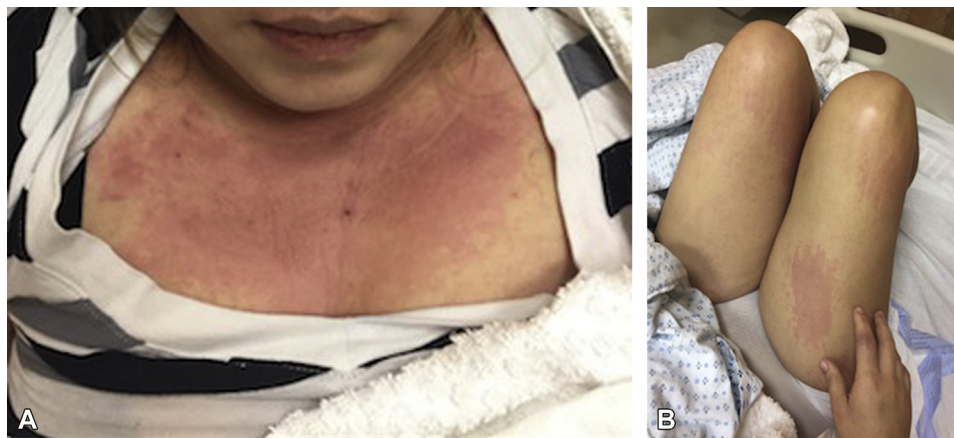


Fig 1. Case 1. **A**, Eczematous plaque with pinpoint necrosis on face and chest. **B**, Linear urticarial papules and plaques on the lower extremities.

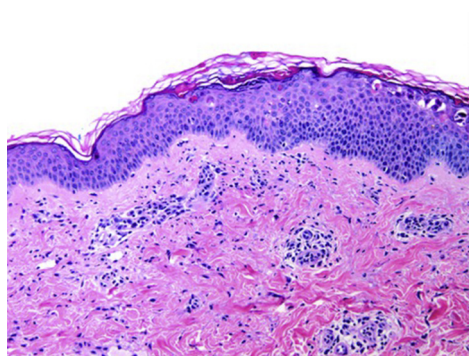


Fig 2. Case 1. Biopsy from chest stained shows isolated necrotic keratinocytes in the upper layers of the epidermis associated with a perivascular neutrophilic infiltrate. (Hematoxylin-eosin stain; original magnification: $\times 20$.)

She re-presented 2 weeks later with fever, arthralgia, upper respiratory infection symptoms, and new rash. Examination illuminated urticarial papules on extremities and erythematous plaques on the upper chest, lower abdomen, and inguinal areas (Fig 3). Some areas had a dusky appearance and pinpoint necrotic crust. Bloodwork again showed leukocytosis, persistently elevated inflammatory markers, abnormal liver functions, and positive human metapneumovirus. Ultrasound scan showed hepatosplenomegaly.

Biopsy of an abdominal plaque found sparse perivascular lymphoid infiltrate and scattered necrotic keratinocytes in the upper epidermis suggesting erythema multiforme (EM) (Fig 4). Direct immunofluorescence was negative. Biopsy from the right forearm rash found superficial perivascular lymphoid infiltrate with absence of neutrophils noted.

Given her constellation of symptoms, the patient sJIA was diagnosed, and the patient was treated with

anakinra, 100 mg/d. She experienced resolution of symptoms and normalization of laboratory values at 5-month follow-up.

DISCUSSION

Still disease is a diagnosis of exclusion based on the Yamaguchi criteria.³ Major criteria include fever for at least 1 week, arthralgia for at least 2 weeks, maculopapular nonpruritic salmon-colored rash, and granulocytic leukocytosis ($\geq 10,000/\mu\text{L}$). Minor criteria include sore throat, lymphadenopathy, hepatomegaly or splenomegaly, abnormal liver functions, and negative RF and ANA. Diagnosis requires 5 features, with at least 2 major diagnostic criteria.

Atypical dermatologic findings make diagnosis especially challenging. Recently, several reports have described atypical cutaneous findings in AOSD, and there are some reports of these findings in cases of sJIA. Common features of atypical Still disease include persistent pruritic papules and plaques.^{4,5} Less common features are urticarial eruptions, generalized nonpruritic erythema, and eyelid edema mimicking dermatomyositis.¹ The histologic features of the transient eruption may be nonspecific, ranging from a predominantly lymphocytic infiltrate to predominantly neutrophilic,² whereas persistent papules and plaques of AOSD show necrotic keratinocytes in the upper epidermis and an infiltrate of lymphocytes and neutrophils in the papillary dermis. Less common findings are basal vacuolar degeneration, nuclear dust, and subcorneal and intracorneal pustules.⁶

Both patients presented with a constellation of findings consistent with Still disease, including the typical evanescent erythematous eruption, but also with eczematouslike plaques with pinpoint necrosis,

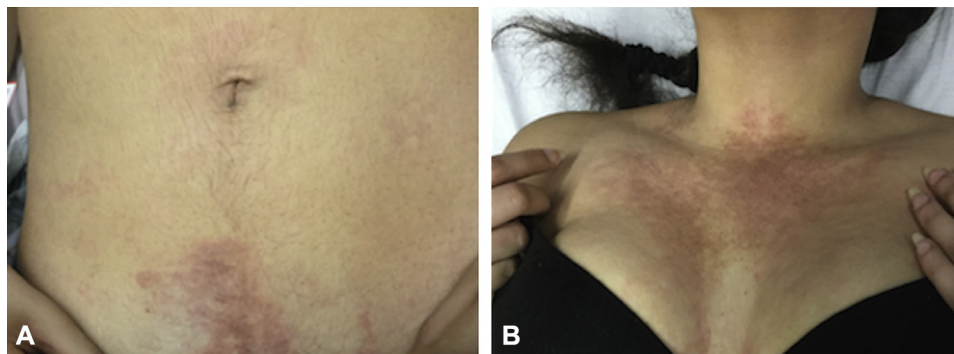


Fig 3. Case 2. Erythematous plaques with pinpoint necrosis on the abdomen and chest.

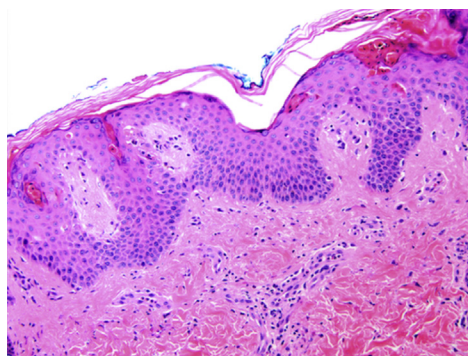


Fig 4. Case 2. Biopsy from lower abdomen shows scattered superficial necrotic keratinocytes in the upper epidermis and associated with sparse perivascular lymphoid infiltrate. (Hematoxylin-eosin stain; original magnification: $\times 20$.)

which initially raised clinical suspicion for dermatomyositis or other connective tissue disease. In both cases, histologic features were initially interpreted as EM, which did not fit the clinical findings. EM is the prototype diagnosis within the histologic differential of necrotic keratinocytes, which also includes Stevens-Johnson syndrome, toxic epidermal necrolysis, lichen planus, lupus, and graft-versus-host disease. Atypical manifestations of Still disease and sJIA must be considered in this differential, as histologic features can closely mimic EM. Ultimately, the identification of necrotic keratinocytes as a feature of atypical Still's disease helped establish the diagnosis. A notable distinction is that in EM the necrotic keratinocytes are scattered throughout the epidermis, whereas in Still disease they are situated in the upper epidermis. Additionally, another piece of evidence is that in the patient biopsies there was no vacuolar interface dermatitis. In EM, one would expect some interface dermatitis.

These cases add to the growing literature of this unusual manifestation of Still disease. There have only

been 2 prior reports of atypical cutaneous manifestations in sJIA comprising 6 patients.^{7,8} The current report adds to this sparse information and further confirms that atypical papules and plaques can be seen in both adult and pediatric disease entities.

Reported associations with atypical Still disease include delayed malignancy⁹ and viral infections including echovirus, rubella, and Epstein Barr virus.¹⁰ Our adult case was preceded by Zika infection, which is the proposed trigger in her case and has not been previously reported in association with Still disease.

These cases highlight that an atypical rash can misguide diagnosis of Still disease, but histologic evidence of necrotic keratinocytes may be a clue to its diagnosis. Clinicians and dermatopathologists should be aware that atypical manifestations of Still disease can histologically mimic EM, and thus should have high suspicion for this diagnosis when EM does not fit the clinical presentation.

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