

# Adult-Onset Still Disease: Persistent Pruritic Papular Rash With Unique Histopathologic Findings

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## PRACTICE POINTS

- Serologic testing and skin biopsy are necessary in the timely and appropriate diagnosis of adult-onset Still disease (AOSD).
- In patients with a persistent pruritic papular rash, consider AOSD if there is a supporting history.
- Skin biopsy is diagnostic of AOSD with the unique histopathologic findings of dyskeratotic keratinocytes in the cornified layers as well as in the epidermis and a sparse neutrophilic and/or lymphocytic infiltrate in the papillary dermis without vasculitis.

Adult-onset Still disease (AOSD) is a systemic inflammatory condition that manifests clinically through spiking fevers, arthralgia, evanescent skin rash, and lymphadenopathy. The most commonly used criteria for diagnosing AOSD are the Yamaguchi criteria. The major criteria include high fever for more than 1 week, arthralgia for more than 2 weeks, leukocytosis, and an evanescent skin rash. The minor criteria include sore throat, lymphadenopathy and/or splenomegaly, liver dysfunction, and negative rheumatoid factor and antinuclear antibodies. Classically, the skin rash is described as an evanescent, salmon-colored erythema involving the extremities. Nevertheless, unusual cutaneous eruptions of AOSD have included persistent pruritic papules and plaques. Importantly, this atypical rash demonstrates specific histologic findings that are not found on routine histopathology of a typical evanescent rash. We describe 2 patients with this atypical cutaneous eruption along with the unique histopathologic findings of AOSD.

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Adult-onset Still disease (AOSD) is a systemic inflammatory condition that clinically manifests as spiking fevers, arthralgia, evanescent skin rash, and lymphadenopathy.<sup>1</sup> The most commonly used criteria for diagnosing AOSD are the Yamaguchi criteria.<sup>2</sup> The major criteria include high fever for more than 1 week, arthralgia for more than 2 weeks, leukocytosis, and an evanescent skin rash. The minor criteria consist of sore throat, lymphadenopathy and/or splenomegaly, liver dysfunction, and negative rheumatoid factor and antinuclear antibodies. Classically, the skin rash is described as an evanescent, salmon-colored erythema involving the extremities. Nevertheless, unusual cutaneous eruptions have been reported in AOSD, including persistent pruritic papules and plaques.<sup>3</sup> Importantly, this atypical rash demonstrates specific histologic findings that are not found on routine histopathology of a typical evanescent rash. We describe 2 patients with this atypical cutaneous eruption along with the unique histopathologic findings of AOSD.

## Case Reports

*Patient 1*—A 23-year-old Chinese woman presented with periodic fevers, persistent rash, and joint pain of 2 years' duration. Her medical history included splenectomy for hepatosplenomegaly as well as evaluation by hematology for lymphadenopathy; a cervical lymph node biopsy showed lymphoid and follicular hyperplasia.

Twenty days later, the patient was referred to the dermatology department for evaluation of the persistent rash.

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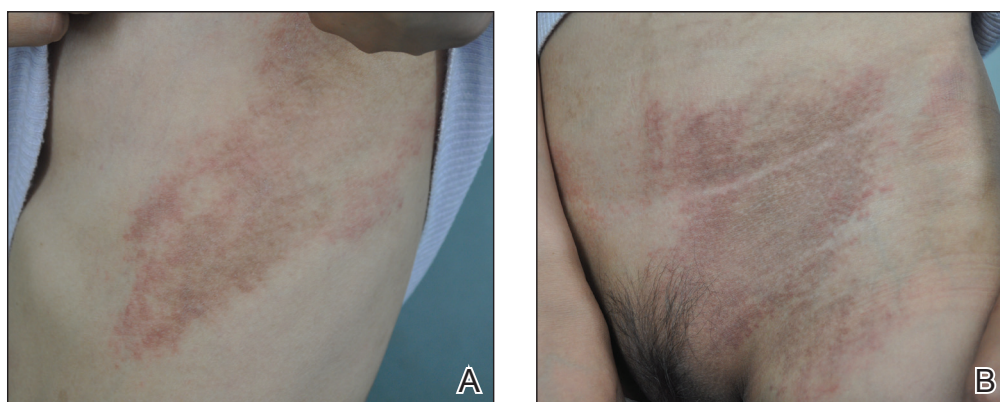
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The patient described a history of flushing of the face, severe joint pain in both arms and legs, aching muscles, and persistent sore throat. The patient did not report any history of drug ingestion. Physical examination revealed a fever (temperature, 39.2°C); swollen nontender lymph nodes in the neck, axillae, and groin; and salmon-colored and hyperpigmented patches and thin plaques over the neck, chest, abdomen, and arms (Figure 1). A splenectomy scar also was noted. Peripheral blood was collected for laboratory analyses, which revealed transaminitis and moderate hyperferritinemia (Table). An autoimmune panel was negative for

rheumatoid factor, antinuclear antibodies, and antineutrophil cytoplasmic antibodies. The patient was admitted to the hospital, and a skin biopsy was performed. Histology showed superficial dyskeratotic keratinocytes and sparse perivascular infiltration of neutrophils in the upper dermis (Figure 2).

The patient was diagnosed with AOSD based on fulfillment of the Yamaguchi criteria.<sup>2</sup> She was treated with methylprednisolone 60 mg daily and was discharged 14 days later. At 16-month follow-up, the patient demonstrated complete resolution of symptoms with a maintenance dose of prednisolone (7.5 mg daily).



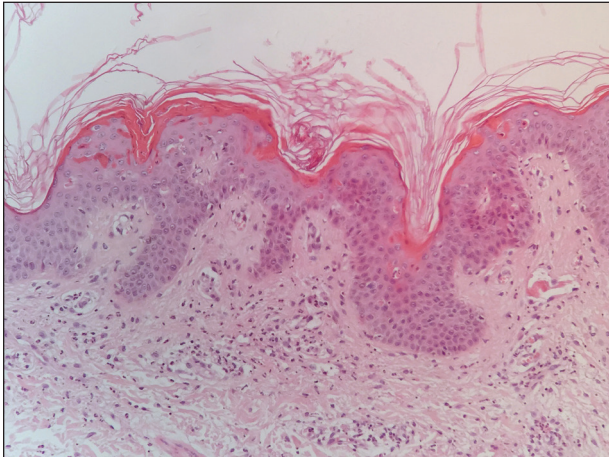
**FIGURE 1.** Clinical presentation of adult-onset Still disease with persistent salmon-colored and hyperpigmented patches over the left hypochondrial region (A) and lower abdomen (B).

### Peripheral Blood Analysis in 2 Cases of Adult-Onset Still Disease

Sample Tested	Patient 1	Patient 2	Reference Range
Alanine transaminase	26 U/L	59 U/L	8–40 U/L
Alkaline phosphatase	78 U/L	139 U/L	15–112 U/L
Antinuclear antibodies	<1:10	<1:10	<1:10
Aspartate aminotransferase	119 U/L	53 U/L	8–40 U/L
C-reactive protein	17.1 mg/L	19.9 mg/L	0–3 mg/L
C3 complement	0.39 g/L	1.71 g/L	0.90–1.80 g/L
C4 complement	0.06 g/L	0.42 g/L	0.10–0.40 g/L
Erythrocyte sedimentation rate	73 mm/h	91 mm/h	0–20 mm/h
Ferritin	488.2 µg/L	14,787.0 µg/L	20–200 µg/L
Hepatitis B panel <sup>a</sup>	Negative	Negative	
Hepatitis C antibodies	0.140 S/CO	0.050 S/CO	<1.000 S/CO
Lactate dehydrogenase	480 U/L	527 U/L	135–226 U/L
Neutrophils	85%	88%	50%–70%
Rheumatoid factor	10.10 IU/mL	10.0 IU/mL	0–15 IU/mL
White blood cell count	15.68×10 <sup>9</sup> /L	7.48×10 <sup>9</sup> /L	4.00–10.00×10 <sup>9</sup> /L

Abbreviation: S/CO, signal-to-cutoff ratio.

<sup>a</sup>Hepatitis B panel included hepatitis B e antibody, hepatitis B e antigen, hepatitis B c antibody, hepatitis B core antigen, and hepatitis B surface antigen.

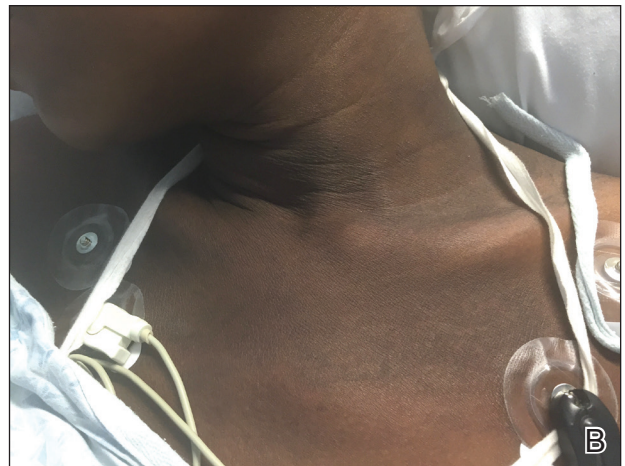


**FIGURE 2.** Histopathology showed superficial dyskeratotic keratinocytes and equivalent perivascular infiltration of neutrophils in the upper dermis (H&E, original magnification  $\times 10$ ).

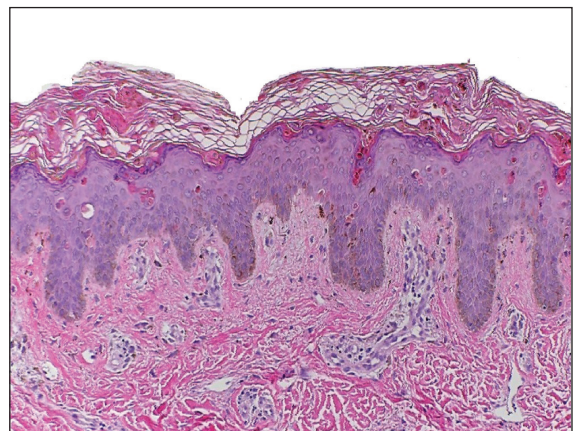
*Patient 2*—A 23-year-old black woman presented to the emergency department 3 months postpartum with recurrent high fevers, worsening joint pain, and persistent itchy rash of 2 months' duration. The patient had no history of travel, autoimmune disease, or sick contacts. She occasionally took aspirin for joint pain. Physical examination revealed a fever (temperature,  $39.1^{\circ}\text{C}$ ) along with hyperpigmented patches and thin scaly hyperpigmented papules coalescing into a poorly demarcated V-shaped plaque on the upper back and posterior neck, extending to the chest in a shawl-like distribution (Figure 3). Submental lymphadenopathy was present. The spleen was not palpable.

Peripheral blood was collected for laboratory analysis and demonstrated transaminitis and a markedly high ferritin level (Table). An autoimmune panel was negative for rheumatoid factor, antinuclear antibodies, and anti-neutrophil cytoplasmic antibodies. Skin biopsy was performed and demonstrated many necrotic keratinocytes, singly and in aggregates, distributed from the spinous layer to the stratum corneum. A neutrophilic infiltrate was present in the papillary dermis (Figure 4).

The patient met the Yamaguchi criteria and was subsequently diagnosed with AOSD. She was treated with intravenous methylprednisolone 20 mg every 8 hours and was discharged 1 week later on oral prednisone 60 mg daily to be tapered over a period of months. At 2-week follow-up, the patient continued to experience rash and joint pain; oral methotrexate 10 mg weekly was added to her regimen, as well as vitamin D, calcium, and folic acid supplementation. At the next 2-week follow-up the patient noted improvement in the rash as well as the joint pain, but both still persisted. Prednisone was decreased to 50 mg daily and methotrexate was increased to 15 mg weekly. The patient continued to show improvement over the subsequent 3 months, during which prednisone was tapered to 10 mg daily and methotrexate was



**FIGURE 3.** Clinical presentation of adult-onset Still disease with hyperpigmented patches and thin scaly papules coalescing into plaques over the back in a V-shaped distribution (A) as well as over the chest in a shawl-like distribution (B), mimicking the typical distribution of cutaneous dermatomyositis.



**FIGURE 4.** Histopathology showed necrotic keratinocytes, singly and in aggregates, distributed from the spinous layer to the stratum corneum. A neutrophilic infiltrate was present in the papillary dermis (H&E, original magnification  $\times 10$ ).

increased to 20 mg weekly. The patient showed resolution of symptoms at 3-month follow-up on this regimen, with plans to continue the prednisone taper and maintain methotrexate dosing.

### Comment

Adult-onset Still disease is a systemic inflammatory condition that clinically manifests as spiking fevers, arthralgia, salmon-pink evanescent erythema, and lymphadenopathy.<sup>2</sup> The condition also can cause liver dysfunction, splenomegaly, pericarditis, pleuritis, renal dysfunction, and a reactive hemophagocytic syndrome.<sup>1</sup> Furthermore, one review of the literature described an association with delayed-onset malignancy.<sup>4</sup> Early diagnosis is important yet challenging, as AOSD is a diagnosis of exclusion. The Yamaguchi criteria are the most widely used method of diagnosis and demonstrate more than 90% sensitivity. In addition to the Yamaguchi criteria, marked hyperferritinemia is characteristic of AOSD and can act as an indicator of disease activity.<sup>5</sup> Interestingly, both of our patients had elevated ferritin levels, with patient 2 showing marked elevation (Table). In both patients, all major criteria were fulfilled, except the typical skin rash.

The skin rash in AOSD, classically consisting of an evanescent, salmon-pink erythema predominantly involving the extremities, has been observed in up to 87% of AOSD patients.<sup>5</sup> The histology of the typical evanescent rash is nonspecific, characterized by a relatively sparse, perivascular, mixed inflammatory infiltrate. Notably, other skin manifestations may be found in patients with AOSD.<sup>1,2,5-16</sup> Persistent pruritic papules and plaques are the most commonly reported nonclassical rash, presenting as erythematous, slightly scaly papules and plaques with a linear configuration typically on the trunk.<sup>2</sup> Both of our patients presented with this atypical eruption. Importantly, the histopathology of this unique rash displays distinctive features, which can aid in early diagnosis. Findings include dyskeratotic keratinocytes in the cornified layers as well as in the epidermis, and a sparse neutrophilic and/or lymphocytic infiltrate in the papillary dermis without vasculitis. These findings were evident in both histopathologic studies of our patients (Figures 2 and 4). Although not present in our patients, dermal mucin deposition has been demonstrated in some reports.<sup>1,13,15</sup>

A 2015 review of the literature yielded 30 cases of AOSD with pruritic persistent papules and plaques.<sup>4</sup> The study confirmed a linear, erythematous or brown rash on the back and neck in the majority of cases. Histologic findings were congruent with those reported in our 2 cases: necrotic keratinocytes in the upper epidermis with a neutrophilic infiltrate in the upper dermis without vasculitis. Most patients showed rapid resolution of the rash and symptoms with the use of prednisone, prednisolone, or intravenous pulsed methylprednisolone. Interestingly, a range of presentations were noted, including prurigo pigmentosalike urticarial papules; lichenoid papules; and dermatographismlike,

dermatomyositislike, and lichen amyloidosis–like rashes.<sup>4</sup> In our report, patient 2 presented with a rash in a dermatomyositislike shawl distribution. It has been suggested that patients with dermatomyositislike rashes require more potent immunotherapy as compared to patients with other rash morphologies.<sup>4</sup> The need for methotrexate in addition to a prednisone taper in the clinical course of patient 2 lends further support to this observation.

### Conclusion

A clinically and pathologically distinct form of cutaneous disease—AOSD with persistent pruritic papules and plaques—was observed in our 2 patients. These histopathologic findings facilitated timely diagnosis in both patients. A range of clinical morphologies may exist in AOSD, an awareness of which is paramount. Adult-onset Still disease should be included in the differential diagnosis of a dermatomyositislike presentation in a shawl distribution. Prompt diagnosis is essential to ensure adequate therapy.

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