

Prurigo pigmentosa as an atypical persistent plaque-like skin rash in adult-onset Still's disease: case report and literature review

Adult-onset Still's disease (AOSD) is a systemic inflammatory disease of unclear etiology. It is classically characterized by spiking fevers, arthralgias, leukocytosis and a typical rash. Usually most of these clinical findings are not specific to this disease and it is often a diagnosis of exclusion. The exception to this is usually the typical maculopapular nonpruritic salmon-colored eruption, which has been shown to have high sensitivity and specificity for the diagnosis of patients with AOSD. It is important to be aware, however, that some patients also present with an atypical rash. Prurigo pigmentosa is a distinctive inflammatory disease first described in Japan. The patient in our case presentation was diagnosed with AOSD based on Yamaguchi criteria and also had a diffuse pruritic persistent hyperpigmented rash on the back, chest and distal extremities with a biopsy revealing histopathology and clinical findings consistent with the diagnosis of prurigo pigmentosa. This review of literature was carried out to examine all the known cases of persistent plaques associated with AOSD. The findings indicated that the histopathologic and clinical findings were similar to those found in prurigo pigmentosa. AOSD can be a chronic debilitating disease if left untreated and can ultimately lead to death. Prurigo pigmentosa may be an under-recognized atypical skin manifestation of AOSD that rheumatologists need to consider in clinical practice.

KEYWORDS: adult-onset Still's disease ■ persistent plaques ■ prurigo pigmentosa ■ pruritic ■ salmon-colored

The classic rash of adult-onset Still's disease (AOSD) is an evanescent, salmon-colored, macular or maculopapular eruption that tends to occur with a fever. The rash predominantly involves the trunk and extremities, but it can also involve the palms, soles of the feet and, occasionally, the face. The cutaneous histopathology in AOSD typically reveals dermal edema and mild perivascular inflammation in the superficial dermis consisting primarily of lymphocytes and histiocytes (FIGURES 1A & B). Immunofluorescence of the skin biopsy may show slight deposition of C3 in the blood vessel walls.

We now present an atypical case of AOSD whose skin presentation manifested as a persistent plaque. The reported rates of persistent eruptions in AOSD patients varied from 25 to 78% [1–3]. A review of all known cases of persistent plaques associated with AOSD demonstrated that prurigo pigmentosa may be associated with AOSD more commonly than previously thought.

Case presentation

A previously healthy 25-year-old Malaysian woman presented to the hospital with a 2-month history of fevers, chills, night sweats,

diffuse myalgia, lethargy and sore throat. She also had a diffuse scaly, dry and pruritic persistent hyperpigmented rash on her back, chest and distal extremities (FIGURES 2A & B). The patient was diagnosed with AOSD based on Yamaguchi criteria (Box 1). Our patient met criteria based on fevers, arthralgias, leukocytosis, sore throat, abnormal liver function tests, inguinal lymphadenopathy and negative antinuclear antibody and rheumatoid factor. No synovitis was found on examination of her peripheral joints. She had extensive infectious workup with negative HIV and respiratory syncytial virus titers, negative bacterial and fungal cultures, and negative stains for malaria. Her urine initially showed microscopic hematuria, but this resolved. Her ferritin levels were elevated up to 7372 ng/ml. Her sedimentation rate was up to 120 mm/h. She had extensive rheumatologic workup including anti-Ro, anti-La, dsDNA, complements, RNP and Smith antibodies that were all normal. Her peripheral blood smear showed moderate normocytic anemia. She had an inguinal lymph node biopsy which was unrevealing. She also had a bone marrow biopsy that showed mildly hypercellular bone marrow with trilineage hematopoiesis. Her PET scan was normal.

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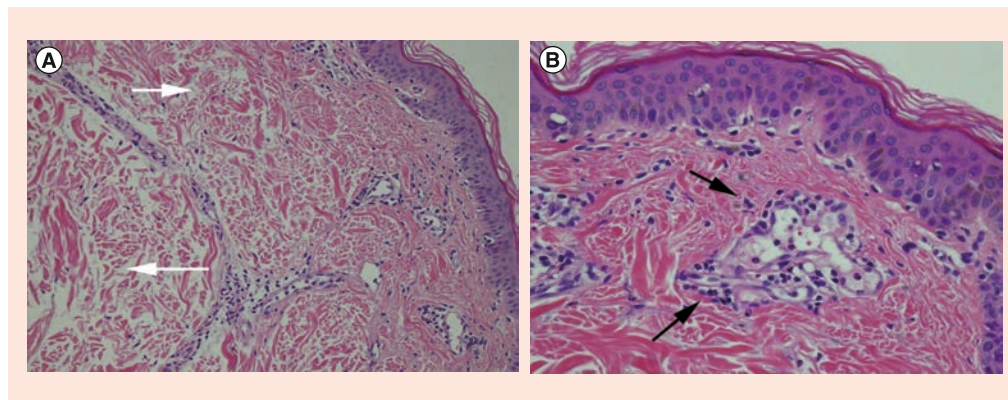


Figure 1. Specimen taken from a 35-year-old patient with Still's disease. The biopsy revealed superficial dermal edema and a mild superficial perivascular infiltrate consisting predominately of neutrophils and histiocytes, consistent with an evanescent eruption of Still's disease. **(A)** This image taken at lower power demonstrates more of the dermal edema (white arrows) while the second image **(B)** demonstrates the perivascular infiltrate of neutrophils and histiocytes (black arrows).

She also had both an endoscopy and colonoscopy with biopsies that were unremarkable. On physical examination, her rash was atypical of the common Still's rash. Because of initial unclear etiology of the atypical rash, the skin biopsies were performed twice. Histologically, the first skin biopsy taken from lesional skin revealed confluent parakeratosis, acanthosis and necrotic keratinocytes identified within all levels of the epidermis. Within the superficial and mid-dermis, a perivascular mixed infiltrate consisting of lymphocytes, neutrophils and a few eosinophils was noted. No cytologic atypia was identified within the infiltrate (FIGURES 3 & 4). A second skin biopsy from lesional tissue was performed 23 days later due to the complexity of the case in the hope that it would help elucidate a cause of the patient's condition. No treatment was initiated during the interim as the diagnosis was unknown at

the time. Histologically, the second biopsy showed acanthosis and mild spongiosis of the epidermis. There was less parakeratosis and fewer necrotic keratinocytes than in the previous biopsy. A perivascular mixed infiltrate within the superficial dermis similar in appearance to the first biopsy was seen. Additionally, melanin pigment incontinence and melanophages were seen within the superficial dermis (FIGURES 5 & 6).

Our patient met criteria for the diagnosis of prurigo pigmentosa based on clinical and histopathologic findings (Box 2). The first biopsy demonstrated several findings seen in fully developed prurigo pigmentosa including: a mixed inflammatory infiltrate, acanthosis with overlying parakeratosis and necrotic keratinocytes. The second biopsy showed continued evolution into a late lesion, as there was marked melanin pigment incontinence and melanophages

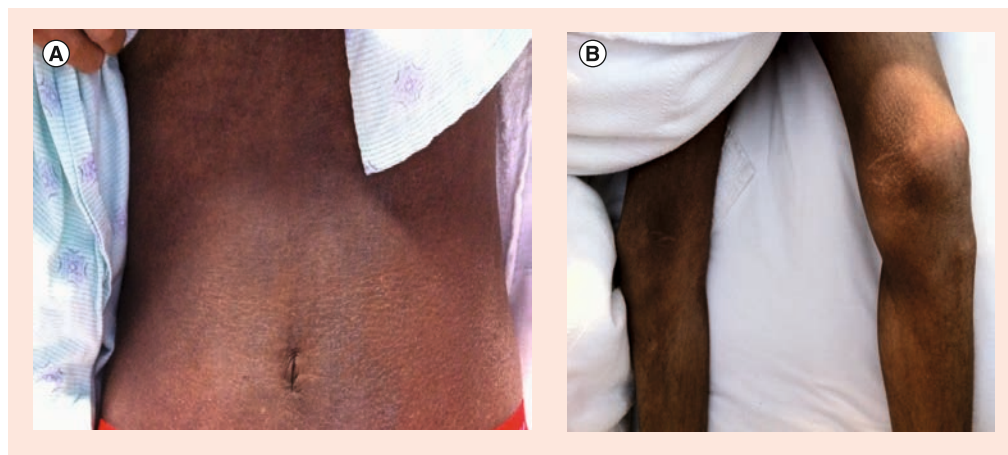


Figure 2. Diffuse scaly, pruritic persistent hyperpigmented rash. Rash on **(A)** abdomen and **(B)** lower extremities of our patient.

identified. Our patient was initially treated with naproxen 500 mg orally two-times a day with no improvement. She was then started on low-dose prednisone 15 mg daily and her fevers and arthralgias improved. She was subsequently discharged from the hospital and initially started on methotrexate 10 mg orally per week. She developed a recurrent episode 1 month later complicated by infection and was placed on high-dose steroids again at 1 mg/kg/day. She then stabilized and was eventually seen in clinic to start on anakinra.

Discussion

The typical salmon-colored evanescent rash is observed in 87% of patients in AOSD with histopathology showing relatively sparse perivascular mixed inflammatory infiltrate containing some neutrophils.

Prurigo pigmentosa is a distinctive inflammatory disease of unknown etiology that was first described by the Japanese dermatologist Masaji Nagashima in 1971 [4]. Clues to diagnosis include a trunk-centered 'scratched urticaria' that usually involves the back, chest and neck, and may also involve proximal extremities and upper extremities. It is rarely diagnosed outside of Japan because of its unfamiliarity. Various mechanisms proposed have been friction, contact allergy, sensitivity to sunlight, endocrine disorders such as diabetes, and metabolic disorders such as ketosis [5]. Prurigo pigmentosa has also been described in association with anorexia nervosa and strict diet, pregnancy, primary biliary cirrhosis and Sjogren's syndrome.

Histologically, the lesions have a distinct appearance and evolve over time depending on the stage at which a biopsy is obtained (Box 2). In early lesions, neutrophils may infiltrate the

Box 1. Yamaguchi criteria.

Four major criteria

- Fever of at least 39°C lasting at least 1 week
- Arthralgias or arthritis lasting 2 weeks or longer
- A nonpruritic macular or maculopapular skin rash that is salmon-colored in appearance and usually found over the trunk or extremities during febrile episodes
- Leukocytosis (10,000 μ l or greater) with at least 80% granulocytes

Five minor criteria

- Sore throat
- Lymphadenopathy
- Hepatomegaly or splenomegaly
- Abnormal liver function studies, particularly elevations in aspartate and alanine aminotransferase and lactate dehydrogenase concentrations
- Negative tests for antinuclear antibody and rheumatoid factor

Data taken from [11].

epidermis and subcorneal collections may be seen. Necrotic keratinocytes are identified throughout all levels of the epidermis. The epidermis becomes spongiotic and a mixed infiltrate, including lymphocytes, neutrophils and eosinophils, is seen in the papillary dermis. As the disease progresses, the epidermis may begin to develop parakeratosis and acanthosis while the mixed inflammatory infiltrate may appear more lichenoid [5]. There is variability in the amount of vacuolar change one sees in the lesions. Melanin pigment incontinence and melanophages may become more prevalent [6]. These late stage lesions are nearly indistinguishable from the postinflammatory hyperpigmentation seen in other diseases. Immunofluorescence studies are invariably

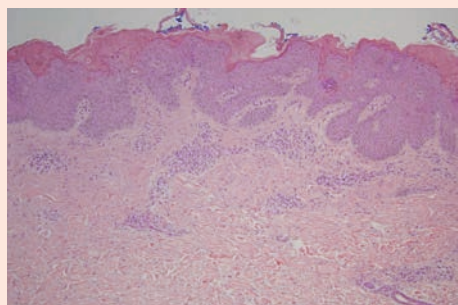


Figure 3. Acanthosis and hyperkeratosis with patchy parakeratosis. Scattered necrotic keratinocytes in all levels of the epidermis were identified.

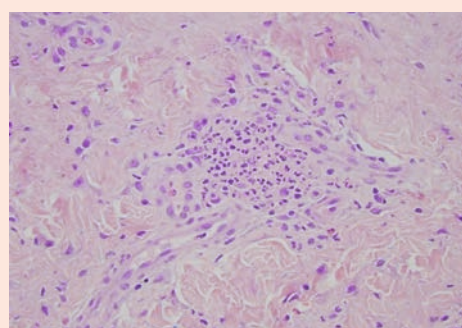


Figure 4. Mixed superficial perivascular infiltrate composed of neutrophils, eosinophils and lymphocytes.

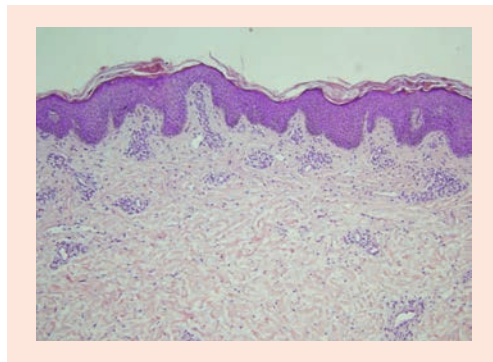


Figure 5. Acanthosis with mild parakeratosis and a superficial perivascular infiltrate.

negative [7,8]. While the cases in TABLE 1 appear to be histologically consistent with a diagnosis of prurigo pigmentosa, it is difficult to definitively determine without seeing the original slides; however, the histological descriptions as well as the clinical findings found in the papers appear to correlate well with different stages of prurigo pigmentosa.

Conclusion

The recognition of an atypical rash seen in patients with a confusing clinical picture as a possible manifestation of AOSD may aid in the diagnosis. Prurigo pigmentosa may be an under-recognized atypical skin manifestation of AOSD that rheumatologists need to consider in clinical practice. The presence of the aforementioned skin lesions, based on our review of the literature and cases, should alert physicians to the possibility of AOSD. Nonetheless, due to the uncommon nature of prurigo pigmentosa in patients with AOSD, these skin lesions should not be considered diagnostic criteria.

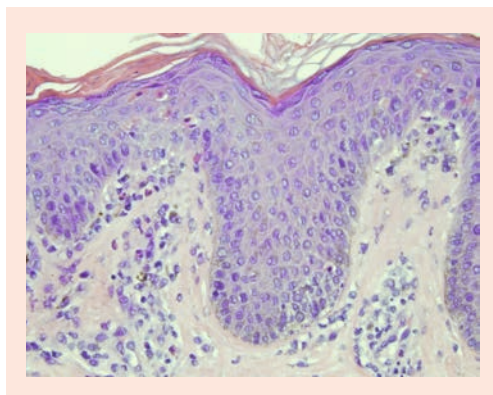


Figure 6. Mild spongiosis and interface changes with scattered necrotic keratinocytes. A mixed inflammatory infiltrate with melanin pigment incontinence and melanophages within the superficial dermis are noted.

Future perspective

There are some similarities in the immunohistochemistry of prurigo pigmentosa and AOSD that may help us understand the treatment of both diseases. Over the next 5–10 years this may provide better insight into potential future therapies for treating both conditions. To date, there have been no studies evaluating doxycycline for treatment of AOSD; these should be considered in the near future. Using immunohistochemistry, a study by Lu *et al.* has shown IL-6 to be more strongly expressed in prurigo pigmentosa skin lesions; the results were statistically significant [9]. Increases in IL-8 were also present. This may explain the potential therapeutic benefits of doxycycline due to its anti-inflammatory action, inhibiting IL-6, IL-8, IL-15, Rantes and IP-10 that normally regulate leukocyte differentiation and tissue inflammation response. Treatment of at least a 2–4 week course of doxycycline at a dose of 200 mg/day has been effective in most cases in initial and recurrent episodes. Other established treatments include minocycline, tetracycline, dapsone, sulfamethoxazole and macrolide antibiotics. In a review article by Mavragani *et al.* it was concluded that many cytokines are involved in the pathogenesis of AOSD including IL-6, IL-8, IL-1, TNF- α , IL-17 and IL-18 [10]. Cytokines involved as potential markers of disease activity include IL-1B and soluble IL-2 receptor. IL-18 has been a marker of disease severity and response to corticosteroids. Atypical skin rash is also linked to more aggressive disease. There are limited data for the treatment of AOSD, however, disease-modifying agents, such as methotrexate, cyclosporine, hydroxychloroquine, gold, penicillamine and azathioprine, as well as biologics, such as anakinra, rilonacept and anti-TNF, are used in refractory disease.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

Box 2. Typical findings of prurigo pigmentosa.**Clinical**

- Distribution of lesions:
 - Symmetrical, especially on the trunk
- Sites of predilection:
 - Back, chest and neck
- Sites rarely involved:
 - Proximal extremities (especially the upper extremities) and forehead
- Sites never involved:
 - Distal extremities, face and mucous membranes
- Individual lesions:
 - Early lesions: urticarial papules and plaques, often scratched
 - Fully developed lesions: papules, papulovesicles, rarely papulopustules with frank vesicles
- Arrangement of lesions:
 - Reticular
- Typical clinical dynamics of the disease process:
 - Papules erupt in crops and subside within a week; recurrences at the same sites are common, often lesions of different ages being present together
- Symptoms:
 - Pruritus of early lesions is often severe, resolving lesions are devoid of symptoms

Histopathologic

- Early lesion:
 - Superficial perivascular infiltrate of neutrophils and possible microabscess formation
 - Edematous papillary dermis with extravasated erythrocytes
 - Spongiosis of epidermis
 - Few necrotic keratinocytes may be present, even early in the course of this disease
- Fully developed lesion:
 - Lymphocytes and eosinophils increase in number while neutrophils are found in variable numbers
 - Epidermal spongiosis is accompanied by ballooning, acanthosis and parakeratosis begin
 - A lichenoid infiltrate may be seen with interface changes
 - Numerous necrotic keratinocytes and necrosis *en masse* are sometimes seen
- Late lesion:
 - Predominately lymphocytic infiltrate
 - Epidermis is slightly acanthotic and parakeratotic
 - Melanin incontinence and melanophages are seen
 - Individual necrotic keratinocytes may be present
- Subtle variations:
 - Features of prurigo simplex may overlay signs diagnostic of prurigo pigmentosa because of intense pruritis associated with onset

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Table 1. Review of 12 articles with persistent papules and plaques.

Case(s)	Clinical & laboratory data	Gross findings	Disease duration	Pruritic	Histology	Pathologic diagnosis	Response to treatment	Ref.
1 (our patient from this article)	ANA negative, RF factor negative, elevated ferritin, normocytic anemia, and leukocytosis	Diffuse persistent hyperpigmented rash on back, chest and distal extremities	2 months	Yes	Hyperkeratosis, mild spongiosis, acanthosis, necrotic keratinocytes, neutrophilic and lymphocytic perivascular infiltrate with melanophages	Prurigo pigmentosa	Complete resolution of rash and systemic symptoms with prednisone 20 mg and started on methotrexate for maintenance	
2	Leukocytosis, elevated LFTs and elevated ferritin	Persistent skin rash on upper chest and back and evanescent skin eruption on lower extremities	3 weeks	N/A	Dyskeratosis, mild acanthosis, slight spongiosis, dense inflammatory infiltrate consisting of lymphocytes, neutrophils, melanophages and eosinophils	Prurigo pigmentosa	Complete resolution of rash with prednisone 40 mg	[12]
3	Leukocytosis, elevated LFTs, elevated ferritin, normocytic anemia, RF and ANA negative	Papular eruption arranged in reticulate pattern and distributed on face, neck, trunk and legs	10 days	Yes	Perivascular neutrophilic and lymphocytic infiltrate within superficial dermis, mild edema	Prurigo pigmentosa	Responded to prednisolone 1 mg/kg/day and then prednisone therapy	[13]
4	Fever, sore throat, arthralgia and itching skin eruptions, neck lymphadenopathy, leukocytosis, elevated AST/ALT, and elevated ferritin	Numerous reticulated, erythematous and brownish pruritic papules and plaques on chest, abdomen and back. Evanescent urticated eruptions occurring with fever	2 weeks	Yes	Parakeratosis, mild acanthosis, some foci of eosinophilic spongiosis, scattered dyskeratotic cells in the upper epidermis, and a mixed dermal perivascular infiltrate composed of lymphocytes, eosinophils and neutrophils	No specific diagnosis	Responded to 3-day course of pulse intravenous methylprednisolone and then oral steroids. Maintenance therapy with methotrexate, hydroxychloroquine and prednisolone	[14]
5	Elevated ESR, negative ANA and RF, elevated ferritin	Papular eruption that then became hyperpigmented papules over thighs, pretibial areas and upper back and forearms	N/A	Yes	Hyperkeratosis, dyskeratosis, necrotic keratinocytes, mild perivascular lymphocytic infiltrate with rare eosinophils, dermal mucin	No specific diagnosis	Initial prednisone therapy with no response then methotrexate and etanercept and switched to IL-1 receptor antagonist (anakinra)	[15]
6	Normocytic anemia, elevated LFTs, and negative ANA and RF	Migratory plaque-like rash on lower legs then became fixed and spread symmetrically on arms, dorsal hands, upper chest and back	8 months	Yes	Mild spongiosis, microabscesses, necrotic keratinocytes, mild dermal edema, lymphocytic and eosinophilic perivascular infiltrate, negative IF	No specific diagnosis	Methylprednisolone for 3 days with resolution of rash and then prednisone oral daily with methotrexate	[16]
7	Anemia, leukocytosis, thrombocytosis, elevated ESR and CRP, elevated ferritin, negative ANA and RF	Generalized salmon-pink, maculopapular and urticarial lesions in arms and chest. Also brownish, nonfollicular papules that coalesced into plaques with irregular borders and discrete, but adherent scales on forehead, neck and back	5 weeks	N/A	Parakeratosis, acanthosis, necrotic keratinocytes, lymphocytic, neutrophilic and histiocytic perivascular infiltrate, negative IF	No specific diagnosis	Rapid resolution of all systemic symptoms with the skin lesions fading within 10 days	[17]

A total of 49 patients with AOSD in the cases reviewed. Three of the histopathologic findings including our case were diagnosed as prurigo pigmentosa, with other cases reported commonly found in different stages of prurigo pigmentosa. See Box 2 for details.

ALT: Alanine aminotransferase; ANA: Antinuclear antibody; AOSD: Adult-onset Still's disease; AST: Aspartate aminotransferase; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IF: Immunofluorescence; LFT: Liver function test; N/A: Not available; RF: Rheumatoid factor.

Table 1. Review of 12 articles with persistent papules and plaques (cont.).

Case(s)	Clinical & laboratory data	Gross findings	Disease duration	Pruritic	Histology	Pathologic diagnosis	Response to treatment	Ref.
8–19	Fever, rash, leukocytosis, elevated ferritin, negative ANA and RF, hepatomegaly and splenomegaly	Erythematous, violaceous, dusky red or brownish, scaly or crusted papules widely distributed. One patient with widespread poikilodermatous and lichenoid lesions mainly on sun-exposed areas	N/A	N/A	Parakeratosis, approximately half had mild acanthosis and spongiosis, necrotic keratinocytes in all biopsies, neutrophilic and lymphocytic perivascular infiltrate ranging from sparse to dense, few biopsies with eosinophils and more established lesions contained melanophages	No specific diagnosis	N/A	[18]
20	Polyarthralgias, fever, rash, sore throat, leukocytosis, elevated ESR, CRP and ferritin	Fixed, pruritic, mildly scaly, pink to erythematous, blanchable plaques on lower back, posterior neck/upper back and upper abdomen	N/A	Yes	Hyperkeratosis, dyskeratosis, mild acanthosis, sparse perivascular lymphocytic and neutrophilic dermal infiltrate with occasional eosinophils	No specific diagnosis	Treatment with anakinra, methotrexate and methylprednisolone resulted in resolution of symptoms and rash	[19]
21	Sore throat, rash, fever, polyarthralgia, elevated LFTs, elevated ESR, CRP and ferritin	Fixed papules and plaques with blanchable erythema and fine scale involving the proximal extremities, back, abdomen and ankles	1.5 months	Yes	Hyperkeratosis, dyskeratosis, mild perivascular lymphocytic inflammatory infiltrate with occasional neutrophils and rare eosinophils	No specific diagnosis	Treatment with prednisone and later methylprednisolone resolved the patient's symptoms and rash	[19]
22	Fevers, rash, polyarthralgia, leukocytosis, elevated ferritin	Classic transient morbilliform Still's rash and persistent, erythematous, slightly scaly papules with somewhat linear configuration on upper back and chest	N/A	N/A	Hyperkeratosis, dyskeratosis, acanthosis, mild perivascular lymphocytic inflammatory infiltrate with scattered neutrophils	No specific diagnosis	Patient died prior to treatment from unrelated causes	[19]
23–49	Fever, rash, arthritis, myalgias, hepatomegaly, elevated ferritin, abnormal liver tests and leukocytosis, negative RF and ANA	Widespread, pruritic, erythematous urticarial or violaceous to brownish flat-topped lichenoid papules over the trunk, neck, face and extensor sides of the extremities	N/A	Yes	Mounds of hyperkeratosis and solitary or cluster necrotic keratinocytes in the superficial epidermis with infiltration of lymphocytes and neutrophils in the upper and mid dermis. Mild acanthosis and spongiosis were noted in approximately half of the specimens	No specific diagnosis	All patients treated with NSAIDs initially and then systemic steroids were used in 27 patients with response. Two patients had immunosuppression with methotrexate and azathioprine with response	[1]

A total of 49 patients with AOSD in the cases reviewed. Three of the histopathologic findings including our case were diagnosed as prurigo pigmentosa, with other cases reported commonly found in different stages of prurigo pigmentosa. See Box 2 for details.

ALT: Alanine aminotransferase; ANA: Antinuclear antibody; AOSD: Adult-onset Still's disease; AST: Aspartate aminotransferase; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IF: Immunofluorescence; LFT: Liver function test; N/A: Not available; RF: Rheumatoid factor.

Executive summary

Adult-onset Still's disease

- It is difficult to make a diagnosis of adult-onset Still's disease (AOSD), due to a lack of pathognomonic histopathological and serological findings.
- The Yamaguchi criteria are the most commonly used, with high sensitivity and specificity. However, it is critical to exclude other infections, inflammatory diseases and malignancies before a diagnosis of AOSD is made.
- The typical salmon-colored evanescent rash is observed in 87% of patients in AOSD, with histopathology showing relatively sparse perivascular mixed inflammatory infiltrate containing some neutrophils.
- More evidence has demonstrated that persistent papules and plaques of AOSD have important diagnostic value and could be related to poorer prognosis and more aggressive refractory disease.
- The reported rates of persistent eruptions in AOSD patients varied from 25 to 78%.
- Our patient with AOSD also had a histopathological diagnosis of prurigo pigmentosa.

Prurigo pigmentosa

- Prurigo pigmentosa is a distinctive inflammatory disease of unknown etiology.
- Histologically, the lesions have a distinct appearance and evolve over time depending on the stage at which a biopsy is obtained.
- As the disease progresses, the epidermis may begin to develop parakeratosis and acanthosis, while the mixed inflammatory infiltrate may appear more lichenoid.
- While the cases in our review of literature of atypical persistent plaques appear to be histologically consistent with a diagnosis of prurigo pigmentosa, it is difficult to definitively determine without seeing the original slides; however, the histological descriptions as well as the clinical findings found in the papers appear to correlate well with different stages of prurigo pigmentosa.

Immunohistochemistry

- IL-1, IL-6, IL-18 and TNF- α have been shown to be associated with AOSD and IL-6 has been shown to correlate with disease activity.
- A statistically significant difference in IL-6 expression has been observed in prurigo pigmentosa skin lesions. Increases in IL-8 were also present.

Treatment

- There are limited data for the treatment of AOSD; however, disease-modifying agents, such as methotrexate, cyclosporine, hydroxychloroquine, gold, penicillamine and azathioprine, as well as biologics, such as anakinra, rilonacept and anti-TNF, are used in refractory disease.
- A novel IL-6 antagonist, tocilizumab, has been proved to be a promising treatment for AOSD.
- Treatment of at least a 2–4-week course of doxycycline at a dose of 200 mg/day has been effective in most cases in initial and recurrent episodes of prurigo pigmentosa.
- Other established treatments for prurigo pigmentosa include minocycline, tetracycline, dapsone, sulfamethoxazole and macrolide antibiotics.

Conclusion

- The recognition of this atypical rash seen in patients with a confusing clinical picture as a possible manifestation of AOSD may aid in the diagnosis and help establish prognosis.
- There are many similarities between the immunohistochemistry between prurigo pigmentosa and AOSD, and more studies need to be done to help us understand and broaden the treatment options of both diseases over the next 5–10 years.
- Prurigo pigmentosa may be an under-recognized atypical skin manifestation of AOSD that rheumatologists need to consider in clinical practice.

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