

ADULT ONSET STILL'S DISEASE AND PRURIGO PIGMENTOSA: An unusual association and review of literature

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SUMMARY

This study was conducted in the Department of Medicine, Department of Dermatology, Al-Adan Hospital, Ministry of Health- Kuwait. This patient was hospitalized as a case of pyrexia of unknown origin. We report atypical skin eruption in this patient who fulfilled the criteria for Adult Onset Still's Disease (AOSD) despite the absence of the typical still's rash. Skin biopsy revealed prurigo pigmentosa (PP). To elucidate this unusual association, we searched the literature for the cutaneous manifestations of AOSD. Kahori T, et al had described PP like lesions in a patient with AOSD in addition to the typical still's rash and it is the only case report that exists in English literature. In our case, except for still's rash, all the criteria of AOSD were present, the diagnosis was made after excluding all other possible causes i.e. infectious diseases, other rheumatic diseases, vasculitis and malignant disease. The objective for reporting this case and review of literature is to shed more light on the rare dermatological disorder Prurigo Pigmentosa (PP) and its unusual association with Adult Onset Still's Disease (AOSD).

Clinicians and dermatologist must be aware of this unusual association of PP and AOSD as the diagnosis of AOSD can be made in the absence of the typical still's rash but in the presence of other atypical cutaneous manifestations including PP.

KEY WORDS: Prurigo pigmentosa, Adult Onset Still's Disease, Still's rash.

Abbreviations: Adult onset still's disease (AOSD). Prurigo Pigmentosa (PP).

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INTRODUCTION

Both prurigo pigmentosa (PP) and adult onset still's disease (AOSD) independently are uncommon diseases. Expectedly the association of PP and AOSD is extremely rare.

PP is a rare dermatosis with unknown etiology.¹ It is seen most commonly among young adult Japanese females.² Clinically, it presents itself as pruritic urticarial papules, papulo-vesicular and vesicles arranged in a reticulate pattern and distributed symmetrically on the face, neck, back, chest and extremities.³ Lesions involute in a matter of days leaving behind net like pigmentation. Exacerbations and recurrences are the rule.⁴

AOSD is an inflammatory disorder used to describe a series of adult patients who did not

fulfill criteria for classic rheumatoid arthritis but had features similar to children with systemic rheumatoid arthritis.^{5,6} To establish a diagnosis of AOSD requires the presence of certain major or minor criteria or a combination of both, and absence of certain exclusions.⁷

Prurigo pigmentosa has been described in association with ketosis related to diabetes mellitus, anorexia nervosa and strict diet,⁸ pregnancy,⁹ primary biliary cirrhosis and Sjorgen syndrome.¹⁰ Kahori T, et al described PP like lesions in a patient with AOSD in addition to the typical still's rash and it is the only case report that exists in English literature.¹¹

We report a second case of prurigo pigmentosa in association with adult onset still's disease in absence of the typical still's rash. As the clinicians and most of the dermatologist are unaware of this unusual association of PP and AOSD, we decided to report this case and to shed more light on both conditions.

CASE REPORT

A 26 - year old Nepali female, a mother of one child with no significant past medical history presented with a ten-day history of daily spiking fever, chills, arthralgias, myalgias and pruritic skin eruption.

On examination, she looked pale, febrile (temperature 39.2°C), had non-suppurative pharyngitis and generalized lymphadenopathy. The lymph nodes were slightly tender, small and discrete. The cardio-respiratory, abdominal and neurological systems were

normal. There was no evidence of active arthritis. The skin eruption was in the form of pruritic papular eruption arranged in a reticulate pattern and distributed symmetrically on the face, neck, trunk and legs (Figs-1a, 1b, 1c).

Investigations: CBC: WBC $13.95 \times 10^9/l$, differential count showed neutrophilic leukocytosis ($11.65 \times 10^9/l$), Hb 10.1g/dl, MCV 82.3 fl (79.4-94.8 fl), MCHC 26.4 pg (25.6-32.2 pg), platelet $314 \times 10^9/l$ (182-369 $10^9/l$), ESR 115mm/hour, C-reactive protein 201ng/l, ASO titer < 200 IU/ml, liver function tests: AST 131 IU/l (0-31), ALT 273 IU/l (0-35), ALP 266 (35-104 IU/l), total bilirubin $15.9\mu\text{mol/l}$ (3-22). S. iron $8.25\mu\text{mol}$ (6.6-26) and S. transferrin 3.91g/l (2.52-4.29) were normal. S. ferritin 2000ng/ml (10-120) was very high.

Coagulation profile was normal. Other biochemical profile including renal profile, lipid profile, S. calcium, S. magnesium, phosphorus were within normal limits. S. pregnancy test was negative. Complete sepsis work-up including throat swab, urine routine, blood culture, thick and thin blood film for malaria, Widal test, Brucella agglutination tests, monospot test, CMV serology, mycoplasma serology, HIV serology, hepatitis serology were all negative. Collagen screen (RA factor, ANA, ANCA, anti-mitochondrial antibody, thyroid autoantibodies) was negative. Screening for occult malignancy (stool for occult blood, tumor markers) was negative.



Fig-1a, 1b & 1c: The skin eruption in the form of papular eruption arranged in a reticulate pattern and distributed symmetrically on the trunk, back and legs.

Chest X-ray, ECG, abdominal ultrasound, echocardiography, intravenous urogram did not reveal any abnormalities. CT scan chest, abdomen and pelvis revealed discrete axillary, para-vascular, aorto-pulmonary, left para-aortic lymphadenopathy. Cervical lymph node biopsy revealed reactive lymphadenitis. Bone marrow examination was consistent with anemia of chronic illness with no evidence of hematological malignancies or lymphomatous infiltration. Skin biopsy was consistent with PP (Figs-2a, 2b, 2c, 2d).

MANAGEMENT

The patient was initially managed conservatively with adequate hydration, acetaminophen tablet, as required. However, she complained of daily spiking fever up to 41°C associated with chills and sweating.

The diagnosis of adult-onset Still's disease was made after excluding the infective, collagen and malignant disorders, supported by the markedly elevated serum ferritin level. The eruption and fever subsided after the administration of prednisolone 1mg/kg/day. It required almost a week for fever to resolve completely. The patient was discharged on a steroid tapering dose. On follow-up, ESR, C-reactive protein and S. ferritin level returned to levels within the normal reference range.

DISCUSSION

The diagnosis of AOSD can be very difficult. There are no specific tests and reliance is usually placed on a symptom complex and the well described typical rash seen in most patients. The classic evanescent rash of still's disease was first noted by Boldero in 1933¹² and is referred to as a still's rash or rheumatoid rash despite the absence of an association with adult seropositive rheumatoid arthritis.

To establish a diagnosis of AOSD requires the presence of certain major or minor criteria or a combination of both, and absence of certain exclusions.⁷

Major Criteria: The proposed major criteria include:-

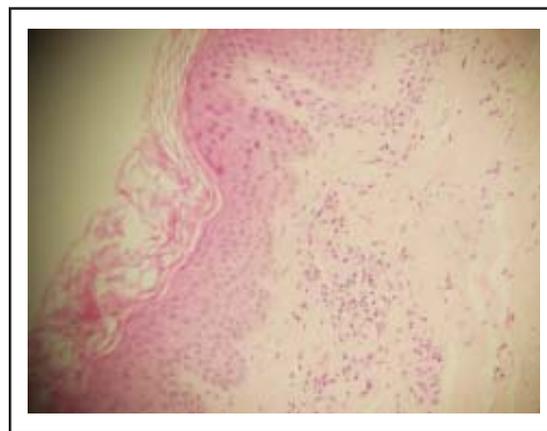


Fig-2a: Mild hyperkeratosis, acanthosis and superficial perivascular infiltrate, the epidermis shows focal mild spongiosis.

- * Fever of at least 39°C lasting one week or longer.
- * Arthralgias or arthritis lasting 2 weeks or longer.
- * Characteristic rash which is a macular or maculo-papular, non pruritic salmon-pink eruption usually apparent over the trunk or extremities during febrile episodes (still's rash).
- * Leukocytosis ($10,000 \times 10^9/l$ or greater with 80% or more granulocytes).

Minor Criteria:

- * Sore throat.
- * The recent development of significant lymph node swelling.
- * Hepatomegaly or splenomegaly.
- * Abnormal liver function studies, particularly

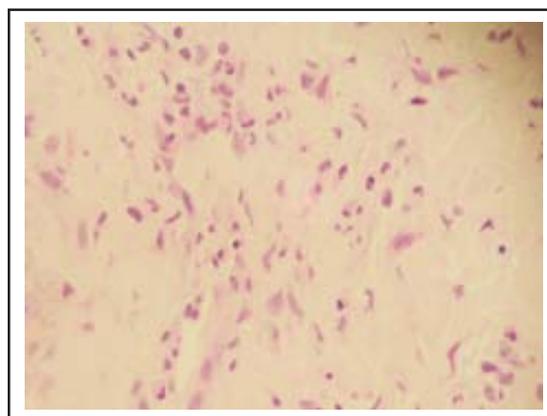


Fig-2b: Perivascular lymphocytic infiltrate admixed with few polymorphs.

aminotransferases and lactate dehydrogenases.

- * Negative tests for anti-nuclear antibody and rheumatoid factor.

Exclusions *Criteria*: The following findings must not be present in AOSD:

- * Infections such as infectious mononucleosis or parvovirus B₁₉.
- * Malignancy, particularly lymphoma.
- * Other rheumatic diseases such as polyarteritis nodosa, systemic lupus erythematosus or rheumatoid arthritis, vasculitis with extra-articular features.

Six sets of criteria have now been proposed for establishing the diagnosis of AOSD.¹³⁻¹⁸ These sets are similar with the difference being the number of major and minor criteria required. A comparison of these six sets of criteria demonstrated that the Japanese criteria had the greatest sensitivity in establishing the diagnosis. The Japanese criteria requires the presence of five features with at least two being major diagnostic criteria.

While 92% of all patients demonstrate some cutaneous manifestations during their illness, the more specific still's rash is seen in 86% of patients with AOSD.¹⁹ Other cutaneous manifestations of AOSD have been reported but these are not well known.

Cutaneous manifestations of AOSD: The common ones are Still's Rash, Koebner phenomenon, Dermatographism.



Fig-2c: Reactive lymphadenitis (X 40): Sinus dilated & prominent showing increased no. of macrophages.

Uncommon: It includes Pruritis, Urticaria, Dermal plaques, Facial Rash, Alopecia, Erythema nodosum and Raynaud's phenomenon.

AOSD has been associated with markedly elevated serum ferritin level in as many as 70% of patients with disease activity and has been suggested as a serologic marker to monitor the response of treatment.²⁰

PP was first described by Nagashima, et al^{21,22} in 1971 in Japan and is diagnosed most commonly in the Japanese population. Less than 40 non-Japanese cases have been published.²³⁻²⁷ Clinically, it presents itself as pruritic urticarial papules, papulo-vesicular and vesicles arranged in a reticulate pattern and distributed symmetrically on the face, neck, back, chest and extremities.³ Lesions involute in a matter of days leaving behind net like pigmentation. Exacerbations and recurrences are the rule.⁴

Histopathologically, PP begins with superficial perivascular infiltrate of neutrophils, shortly thereafter, neutrophils are scattered in dermal papillae and then sweep rapidly through an epidermis in which spongiosis, ballooning and necrotic keratocytes are accompaniments. Very soon eosinophils and lymphocytes come to predominate over neutrophils in a dermal infiltrates that assumes a patchy lichenoid pattern. Intraepidermal vesiculation follows on spongiosis and ballooning and sometimes subepidermal vesiculation on vacuolar alteration at the dermo-epidermal

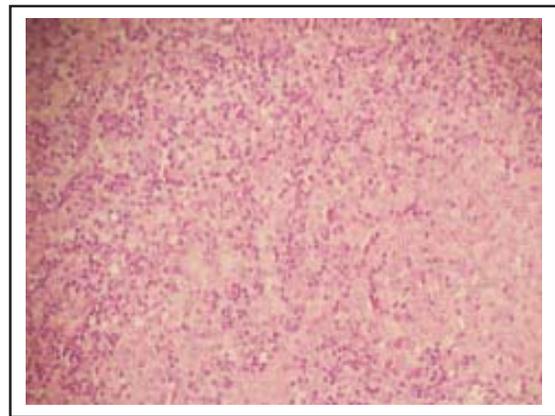


Fig-2d: Reactive lymphadenitis (X 10): Partial loss of architecture. Sinus dilated and prominent with peripherally situated reactive lymphoid follicles.

junction. As the epidermis becomes hyperplastic, parakeratotic and slightly hyperpigmented melanophages begin to appear in the dermis. Studies by immunofluorescence are negative invariably.²⁴

Prurigo pigmentosa has been described in association with ketosis related to diabetes mellitus, anorexia nervosa and strict diet,⁸ pregnancy,⁹ primary biliary cirrhosis and Sjorgen syndrome.¹⁰ To diagnose PP with surety in a patient, clinico-pathologic correlation is often necessary. Diseases to be considered in the clinical differential diagnosis at an early stage of the process are early stages of dermatitis herpetiformis, linear IGA dermatosis, and acute lupus erythromatosis, even though the trunk-centered distribution of lesions and the reticular arrangement of individual lesions in PP allow differentiation. At a resolving stage of the process, PP may be confused with reticular pigmented papules of confluent and reticulated papillomatosis of Gougerot and Carteaud, but in contrast to those lesions, pigmented macules of PP are not keratotic.

Differential Diagnosis: Diseases that have to be considered in the differential diagnosis histopathologically vary according to the stage of the disease process. Early in the course, urticaria, an early manifestation of leukocytoclastic vasculitis, dermatitis herpetiformis, linear IGA dermatosis, acute lupus erythromatosis, eruptive psoriasis, or dermatophytosis may be considered because of the predominance of neutrophils in the infiltrate, but epidermal changes typical of PP, such as spongiosis combined with ballooning, scattered neutrophils in the epidermis, and or necrotic keratinocytes in the absence of features diagnostic of any of the conditions mentioned usually enable differentiation. A fully developed lesion of PP has to be differentiated from erythema multiforme and Mucha-Habermann disease. Neutrophils in collections beneath the cornfield layer and few eosinophils in the infiltrate are clues to the diagnosis of PP. At a late stage of the process, histopathologic features of PP are indistinguishable from any other disease that resolves with postinflammatory hyperpigmentation.

With clinicopathologic correlation, however, the disease may still be diagnosed with certainty because of the typical netlike distribution of pigmentation concerned on the trunk.²⁸

Treatment: Several medications are available for treatment of PP, minocycline and dapsone being used most commonly. Both medications have in common antibiotic and anti-inflammatory effects and they are especially effective in the inhibition of migration of neutrophils, a mechanism that may explain their efficacy in PP. A recent report highlights favorable response of PP to isotretinoin, the mechanism of action of this medication being opaque.²⁷ Many patients also experience spontaneous resolution of the eruption after a few weeks, recurrences occurring only months or years later.

Kahori T, et al described PP like lesions in a patient with AOSD in addition to the typical still's rash and it was the only case report exists in English literature.¹¹ In this case, the patient developed PP-like lesions in addition to the typical rash of AOSD. In our case, except for still's rash, all the criteria of AOSD were present, with support from highly raised serum ferritin level, the diagnosis was made after excluding all other possible causes i.e. infectious diseases, other rheumatic diseases, vasculitis and malignant disease.

CONCLUSIONS

The diagnosis of AOSD can be made in the absence of the typical still's rash but in the presence of other atypical cutaneous features. Therefore, we should carefully follow the clinical course of a patient in order not to overlook these atypical cutaneous manifestations of ASOD.

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