Dermato-Pathologic Clues To Diagnosis Of Adult Onset Still Disease: A Case Report

Abstract

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory condition classically consists of high spikes of fever, morbilliform evanescent skin rash, arthritis, neutrophilic leukocytosis, and multiple organ involvement. However, atypical form of skin rashes has been described with few specific clinical and histopathological patterns that can help in making the diagnosis. A 25-year-old female presented with high spikes of fever, severe debilitating arthritis of peripheral joints, and dusky erythematous flagellate rashes over trunk and proximal limbs. Skin punch biopsy from the cutaneous lesion revealed dyskeratotic keratinocytes in upper epidermis and stratum corneum along with acute inflammatory infiltrate in the dermis: a finding that recently has been found to be constantly associated with this specific pattern of rash of AOSD. The presence of necrotic keratinocytes in upper epidermis and a dermal infiltrate of neutrophils along with characteristic clinical scenario may facilitate earlier diagnosis of AOSD.

Keywords: *Histopathology, necrotic keratinocytes, skin rash, Still's disease*

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Background

Adult onset Still's disease (AOSD) is an acute, systemic inflammatory disorder with unknown etiology. Its classic features are high spiking fever, neutrophilic leukocytosis, seronegative arthritis, and an evanescent salmon-pink skin rash. Other clinical features of lymphadenopathy, myalgia, hepatosplenomegaly, and cardiopulmonary symptoms are also seen.[1] Skin lesions sometimes provide an important clue toward diagnosis. Recently few atypical forms of skin rashes have been described with specific histopathological patterns.[2]

Case Presentation

A 25-year-old female had recurrent high spikes of fever along with moderate joint pain involving bilateral wrists, elbows, knees, and small joints of hands along with generalized weakness for last 3 months. She was not responsive to antibiotics or anti-inflammatory drugs. She had splenomegaly but no hepatomegaly, lymphadenopathy, or respiratory complaint. Her investigations revealed anemia (Hemoglobin-9 g/dL), raised erythrocyte sedimentation rate of 48 mm, total leucocyte count of 14,060 cells/mm^3 (mild leukocytosis), with a differential count comprising 73% of neutrophils, and platelets count of 2.7 lac/mm^3. Her serology was negative for rheumatoid factor (RF) and antinuclear antibodies (ANA). Peripheral smear revealed RBCs with predominantly microcytic hypochromic appearance along with few target cells and polychromatophils. To look for a cause for anemia and splenomegaly, bone marrow aspirate was done which revealed a mild increase in megakaryocytes with focal clustering and occasional hemophagocytosis. Iron stain from the bone marrow aspirate slides revealed increased iron stores (4+) [Figure 1a-d].

After 3 months of onset of symptoms, a dermatology consultation was taken for a persistent itchy rash over trunk. There were dusky erythematous, scaly, barely elevated plaques over back, abdomen, and arms. At the periphery of the plaques, linear lesions were seen giving flagellate appearance [Figure 2]. Considering the typical flagellate rash and associated systemic complaints, the possibility of connective tissue disease, AOSD was considered.

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Skin punch biopsy was taken from the linear rash over back. Histopathological examination showed epidermis with orthokeratosis, mounds of parakeratosis, fibrin plugging, dyskeratotic keratinocytes in stratum spinosum, basal vacuolar degeneration, and focal lymphocytic exocytosis. The underlying papillary dermis showed moderate perivascular mixed inflammatory infiltrate comprising lymphocytes, neutrophils, and nuclear debris along with pigment incontinence. Colloidal iron stain for mucin was weakly positive [Figure 3a-d]. The features were compatible with cutaneous manifestations of AOSD described in recent literature.

Following which she was advised for serum ferritin which was raised 15,504 ng/mL (normal: 30–400 ng/mL). Overall, it fulfilled the Yamaguchi's criteria of ASOD [Table 1].[3] She was then treated with 0.5 mg/kg prednisolone and 10 mg methotrexate for 1 month and is improving on follow-up with disappearance of fever, subsidence of cutaneous lesions [Figure 4], and significant decrease in joint pain.

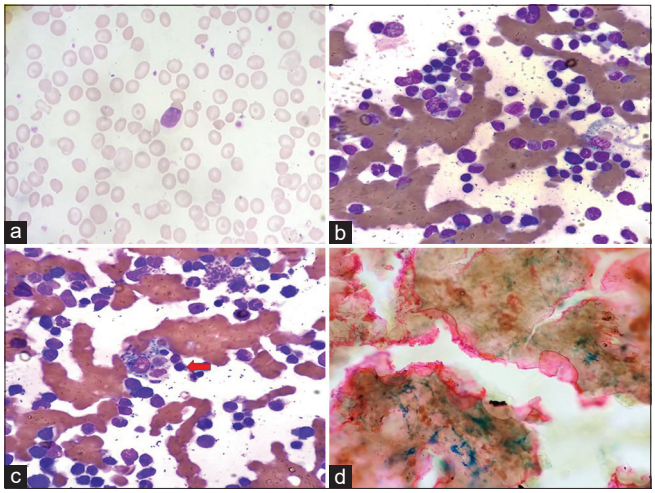

Figure 1: (a) Peripheral smear was unremarkable (Leishman Stain, ×400). (b) Bone marrow aspirate smear showing mild increase in megakaryocytes with focal clustering. (c) Occasional hemophagocytosis was seen (arrow) (Giemsa stain, ×400). (d) Iron stain from the bone marrow aspirate slides revealed increased iron deposit (4+) (Perl's stain, ×100)

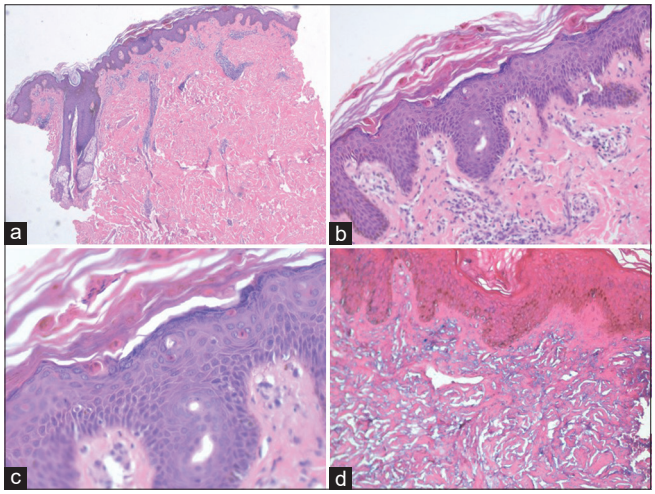

Figure 3: (a and c) Skin punch biopsy is showing epidermis with orthokeratosis, mounds of parakeratosis, fibrin plugging, and stratum spinosum showing dyskeratotic keratinocytes. (b) The papillary dermis shows moderate perivascular mixed inflammatory infiltrate comprising lymphocytes, neutrophils, and nuclear debris along with pigment incontinence. (d) Colloidal iron stain for mucin was weakly positive (H & E, ×40, ×100 & ×400; Colloidal iron, ×100)

Discussion

In 1897, George Frederick Still had first described a type of arthritis that was distinct from rheumatoid arthritis among a group of children[4] and hence the condition is named after him. Still's disease is currently considered an uncommon systemic inflammatory disorder with uncertain pathogenesis. It is characterized by spikes of fever, arthralgia, salmon-colored pink rashes, and leukocytosis with neutrophilia during episodes of fever.[2,5] Other features which might be seen in some patients include sore throat, pericarditis, liver abnormality, splenomegaly, lymphadenopathy, and renal dysfunction. Rheumatoid factor and ANA tests are negative. Association with reactive hemophagocytic syndrome is also reported in literature.[6,7]

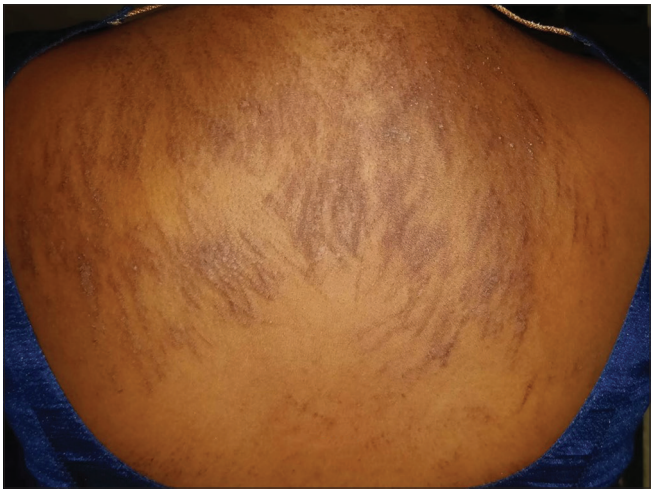

Figure 2: Hyperpigmented slightly scaly lesions on back

Figure 4: Reduction in intensity and number of scaly lesions

There can be varied clinical presentation and a spectrum of differential diagnosis, i.e., neoplasia, infection and other autoimmune disorders which need to be excluded before making the diagnosis of AOSD. Yamaguchi's criteria are the most widely used with >90% sensitivity and specificity apart from the various other diagnostic criteria reported in literature [Table 1].[8-10]

The disease is commoner in young females; however, elderly people might also be affected. Laboratory investigations have shown an increased systemic inflammatory response characterized by increased erythrocyte sedimentation rate, total leucocyte counts, C-reactive protein, dehydrogenase levels, serum ferritin, and abnormal coagulation profile along with abnormal liver function. The serum concentration of glycosylated ferritin is reported to be significantly lower.[7]

With an unknown etiology, various viruses and microbial agents have been proposed to be the triggering factors. Some literature suggested that autoimmune mechanisms such as macrophage activation and inflammatory cytokines (e.g., IL-1, IL-6, IL-18, IFN-δ, and TNF-α), genetic factors, and infection may play a role in the pathogenesis of AOSD.[1,2] It has the classic transient salmon-pink maculopapular rash coexisting with daily high spiking fever.[1,2] Atypical rashes have also been reported, such as urticaria, persistent purpuric papules and plaques, dermographism or linear pigmentation, generalized erythema, vesiculopustular lesions on hands and feet, dermatomyositis-like plaques, prurigo pigmentosa-like plaques, and lichen amyloidosis-like hyperpigmented plaques. Recent studies have postulated that the pathophysiology of dermographism might be an under-reported symptom of the Koebner phenomenon or related to mast cell degranulation.[11]

No pathognomonic histopathology is identified for AOSD. However, our review of the literature revealed few distinctive findings of the biopsy specimens from persistent papules and plaques. The features are epidermal parakeratosis, scattered necrotic keratinocytes mostly in the upper half of the epidermis and interstitial to perivascular neutrophilic infiltration in the papillary dermis with no evidence of vasculitis. On the other hand, the histopathology from urticarial evanescent rash shows normal epidermis, sparse perivascular, and interstitial neutrophilic infiltration with dermal edema.[2,7,12]

Table 1: Yamaguchi's criteria for a classification of adult-onset Still's disease[3]

Major criteria	1. Fever of ≥39°C, lasting for ≥1 week
	2. Arthralgia lasting ≥2 weeks
	3. Typical salmon-pink rash appearing during fever
	4. Leucocytosis (×10,000/mm^3), including 80% more of granulocytes
Minor criteria:	1. Sore throat
	2. Lymphadenopathy and/or splenomegaly
	3. Liver dysfunction
	4. Negative RF and negative ANA
Exclusion	1. Infections
	2. Malignancies
	3. Rheumatic disease

Note: Criteria for calling Still's disease requires ≥5 criteria including ≥2 major criteria.

Diagnosis is usually made after exclusion of infection, autoimmune diseases, and hematologic malignancy. Yamaguchi's criteria which included clinical and biochemical parameters are commonly used for diagnosis.[3] A negative RF and ANA have been reported in literature with 93%–100% accuracy.[1] Serum ferritin is usually higher in patients diagnosed with AOSD. A value of 5 times above a normal level (normal range 30–400 ng/mL or above 1000 ng/mL) has been more suggestive of AOSD, but with only 41%–46% specificity. High serum ferritin level has been reported to be associated with disease activity, chronic recurrent flares, and reactive hemophagocytic lymphohistiocytosis.[1,6] In a study done by Zeng *et al*.[13] the patient had elevated serum ferritin level, pleuritis, interstitial pneumonia, and unrecovered fever persisting after prescribing prednisolone 1 mg/kg/day for 3 days, foretelling poor prognosis.

The treatment of AOSD is dependent on the severity of disease. Steroids are useful in active disease and remission. NSAIDs help in curing mild cases, articular symptoms, and fever.[1] Steroid sparing agents like methotrexate and hydroxychloroquine have also been tried with effectiveness[14] and were also used in our case with good response.

Conclusion

To conclude, a complete and careful evaluation of skin lesions with proper site selection for biopsy and histopathological examination is very important for early diagnosis and outcome in patients with AOSD.

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Conflicts of interest

There are no conflicts of interest.

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