CASE REPORT

Typical evanescent and atypical persistent polymorphic cutaneous rash in an adult Brazilian with Still’s disease: a case report and review of the literature

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Abstract Adult onset Still’s disease (AOSD) is a systemic auto-inflammatory condition of unknown etiology, characterized by high fever, an evanescent, salmon-pink maculopapular skin rash, arthralgia or arthritis and leukocytosis. AOSD can also present with atypical cutaneous manifestations, such as persistent pruritic coalescent papules or plaques and linear lesions that have highly distinctive pathological features and are usually associated with severe disease. Herein, we present a 31-year-old Brazilian man with both typical Still’s rash and atypical persistent polymorphic cutaneous manifestations associated with severe systemic inflammatory response syndrome. Eosinophils that are consistently lacking in the AOSD-associated skin lesions were evident in the skin biopsy of the persistent atypical cutaneous manifestations and were either drug-related or AOSD-associated.

Keywords AOSD · Systemic inflammatory response syndrome · Eosinophils · Atypical cutaneous manifestations

Introduction

Adult onset Still’s disease (AOSD) is a systemic auto-inflammatory condition of unknown etiology, characterized by intermittent spiking high fever, an evanescent, salmon-pink or erythematous maculopapular skin rash, arthralgia or arthritis and leukocytosis with at least 80 % neutrophils [1]. Other common symptoms include sore throat, lymphadenopathy, hepatomegaly, and splenomegaly [2]. High serum ferritin levels, elevated ESR and high CRP levels, absent antinuclear antibody (ANA) and rheumatoid factors (RF) are the most common laboratory findings [3, 4]. We report a case of AOSD in a 31-year-old Brazilian man presenting with both typical Still’s rash and atypical non-evanescent polymorphic cutaneous manifestations.

Case presentation

A 31-year-old Brazilian male presented with high quotidian fever and night sweats, non-productive cough, lower back pain and erythematous rash for two weeks. The fever occurred almost daily and ranged from 39 to 40 °C. The rash started from both hands and was characterized by multiple erythematous confluent roundish macules and papules that coalesced to form large, irregular erythematous plaques (Fig. 1). The rash lasted for a few days and then appeared with a different morphology on the flexor surfaces of his arms as an extensive erythematous linear urticarial eruption (Fig. 2a). Subsequently the rash appeared on his upper and lower trunk as multiple intensely pruritic linear urticarial streaks (Fig. 2b). Ibuprofen has been used intermittently to alleviate back pain as well as the fever with minimal relief. He denied any contacts with sick individuals, insect or animal bites and his last trip was
to Brazil 10 months ago. He has been sexually active in a monogamous relationship.

On admission, his temperature was 39 °C and a persistent pigmented plaque V shaped was evident on his anterior chest extending down the midline to the umbilicus (Fig. 3). Further skin examination revealed a confluent salmon-pink papular eruption on his lower back area and a persistent pigmented plaque on the upper area of his back. Besides mild splenomegaly and a tender right wrist, left second and third proximal interphalangeal joints with no signs of swelling or erythema, the rest of the physical exam was unremarkable. Laboratory profile revealed severe neutrophilic leukocytosis (30,000, normal values 4800–10,800/μL), and a highly elevated serum ferritin levels (>10,000, normal values 17.90–464.00 ng/mL). Autoantibodies (including ANA, ANCA, RF and anti-CCP) were negative. Blood cultures excluded common viral and bacterial infections and RPR were negative. Serological tests for Hepatitis B and C, HIV, Epstein-Barr and Cytomegalovirus were negative. *Borrelia burgdorferi, Bartonella henselae, Rickettsia typhi, RMSF, Typhus* and Parovirus B-19 serologies were negative as well. Parasites for malaria or *Babesia microti* were undetectable on peripheral blood smear. Transthoracic echocardiogram was negative for vegetations and computed tomography (CT) of the neck, chest and abdomen revealed only borderline mild splenomegaly.

The clinical and laboratory findings were consistent with the diagnosis of AOSD according to Yamaguchi criteria [2]. He was started on 50 mg of prednisone. After 2 weeks of treatment, he returned to our hospital with very high daily spiking fever up to 39.5 °C, perfuse sweating, hypotension, elevated liver enzymes and severe leukocytosis with neutrophil predominance. No new skin lesions were noted. The patient was admitted to intensive care unit due to suspected systemic inflammatory response syndrome and was started on broad-spectrum antibiotics and intravenous fluids. Since the blood cultures were negative, antibiotics were discontinued. Anakinra 100 mg daily subcutaneously was added to 50 mg of prednisone with dramatic resolution of his febrile episodes. The patient was discharged with instructions to gradually taper prednisone.

After 1 week of treatment with Anakinra and while on 40 mg of prednisone the patient remained afebrile but new erythematous plaques appeared on lower abdominal quadrants and a skin biopsy was performed (Fig. 4). Skin biopsy showed a normal epidermis, with an inflammatory infiltrate in the dermis surrounding superficial blood vessels and adnexal structures, and the interstitium as well (Fig. 5a). The inflammatory infiltrate composed of lymphocytes, neutrophils and eosinophils (Fig. 5b). Because of the persistent cutaneous manifestations, the patient was...
advised to apply on the persistent eruptions of his chest and abdomen triamcinolone cream 0.5 % twice daily. After 1-month follow-up, the skin rash on the above areas almost resolved.

Discussion

Review of literature, via the PubMed search, using the terms adult onset Still’s disease, cutaneous manifestations and eruptions from 1985 to 2014 to retrieve data on the diversity in clinical manifestations and histopathological findings of polymorphic Still’s rash, was performed (Table 1). AOSD is a rare young adult systemic autoimmune disorder with diverse clinical manifestations and occasionally unwanted serious organ damage like acute liver failure, adult respiratory distress syndrome, disseminated intravascular coagulation, and hemophagocytic syndrome [5–10]. Thus, early recognition of AOSD is crucial and should be always considered in the differential diagnosis of a systemic inflammatory syndrome, particularly when extensive microbiological workup is negative.

The typical skin rash of AOSD is an evanescent salmon-pink non-pruritic or mildly pruritic maculopapular rash, with nonspecific histologic characteristics comprised of a superficial perivascular lymphocytic and scattered neutrophilic infiltrate in the upper epidermis [11–13]. The lesions often develop on the extremities and over the trunk during the peak of the fever and then resolve. AOSD can also present with various atypical cutaneous manifestations and persistent pruritic eruptions (PPEs) are common [14].

PPEs are polymorphic both in morphology and distribution patterns. The more common patterns include lichenoid, linear and dermographism-like eruptions [14], persistent pruritic coalescent papules and plaques [15–17] with linear pigmentation [18], dermal and mucosal hyperpigmentation [19], amyloidosis-like skin eruption [20], generalized peau d’orange appearance of the skin [21], generalized persistent erythema [22], prurigo pigmentosa-like eruption [23, 24], vesiculopustules [25], urticaria [26, 27] and fixed papular lesions [28]. The latter are characterized by atypical wheals, present for more than 24–36 h, with symmetrical distribution [29, 30]. Pruritic lesions are usually evident with the presence of linear dermographism from scratching, as was evident in our patient. The most common atypical rash manifestation in AOSD includes the persistent pruritic coalescent papules and plaques and linear lesions [31].

In addition to the typical maculopapular evanescent Still’s rash, our patient had also an atypical persistent pigmented eruption manifested with different cutaneous morphology and geographic distribution over his body. The linear urticarial streaky and dermographism-like eruptions on upper extremities and torso sequentially gave place to persistent erythematous plaques on his chest and abdomen. We believe that this type of polymorphic cutaneous eruption may be a predictor of severe systemic inflammatory disease like in our case, and could be associated with activation of macrophages and natural killer cells in

Fig. 4 Atypical persistent pruritic eruption: edematous erythematous plaques on lower abdominal quadrants. Stich denotes the site of skin biopsy

Fig. 5 a Hematoxylin and eosin (H&E) stain showing periadnexal and perivascular infiltrate of inflammatory cells surrounding blood vessels, hair follicles and the interstitium (in between the vessels and adnexal structures). Original magnification at ×100. b H&E stain showing perivascular inflammatory infiltration of lymphocytes, neutrophils and eosinophils. Original magnification at ×400
| Author/Year | No of patients/age (range) | Sex | Clinical presentation | Laboratory findings | Cutaneous manifestation | Skin Histology | Treatment |
|-------------|---------------------------|-----|-----------------------|---------------------|------------------------|----------------|-----------|
| Wouters et al. [12] | 1/66/F | F | Polyarthritis, fever, splenomegaly | Leukocytosis, anemia, increased ESR and liver enzymes | Evanescent macular nonpruritic rash on trunk, limbs | Perivascular infiltrate in upper dermis and dermal mucin | NSAIDs, Penicillamine |
| Phillips et al. [21] | 1/51/F | F | Arthralgia, sore throat, lethargy, night sweats | Leukocytosis, anemia, increased ESR, liver enzymes & ferritin | Evanescent erythematosus maculopapular pruritic rash on trunk, limbs, face | Edema of the upper dermis with perivascular neutrophils and eosinophils | NSAIDs, Methotrexate |
| Tay et al. [27] | 1/33/F | F | Fever, arthralgia, malaise, sore throat, headache, lymphadenopathy, hepatomegaly | Leukocytosis, anemia, increased ESR, CRP & immunoglobulins | Evanescent urticarial-like erythematous maculopapular pruritic rash on trunk, limbs | Edema of the upper dermis with perivascular neutrophils and eosinophils | NSAIDs, Prednisolone |
| Setterfield et al. [30] | 1/32/F | F | Arthralgia, sore throat, fever, anorexia, weight loss | Leukocytosis, anemia, increased ESR, CRP & ferritin | Persistent urticarial annular pruritic lesions on trunk and limbs | Nonspecific neutrophilic infiltrate | NSAIDs |
| Lubbe et al. [33] | 1/16/F | F | Fever, arthritis, sore throat, pericardial effusion, hepatomegaly | Leukocytosis, anemia, increased ESR, CRP & ferritin | Evanescent maculopapular lesions on chest, persistent brownish papules and plaques on face, neck, back | Parakeratosis and acanthosis | NSAIDs, Prednisone |
| Salaffi et al. [36] | 1/55/F | F | Fever, arthralgia, fatigue | Leukocytosis, anemia, increased ESR, CRP & ferritin | Urticarial pruritic rash on trunk, limbs and face | Dermal edema with perivascular neutrophilic infiltrate | NSAIDs, Prednisone, Methotrexate |
| Suzuki et al. [18] | 1/25/M | M | Fever, arthralgia, fatigue | Leukocytosis, anemia, increased ESR, CRP & ferritin | Persistent papules and plaques on trunk, linear pigmentation on chest and back | Perivascular infiltrate of dermal vessels with eosinophils and lymphocytes | NSAIDs, Prednisone |
| Perez et al. [43] | 1/39/M | M | Polyarthritis, sore throat, fever, chills, lymphadenopathy, hepatomegaly | Leukocytosis, increased ESR, CRP & liver enzymes & ferritin | Erythematous papules and plaques on neck, face, limbs | Mild perivascular infiltration of dermal neutrophils and eosinophils | NSAIDs, Prednisone, Methotrexate |
| Lee et al. [25] | 1/46/F | F | Arthralgia, high fever, headache, muscle, splenomegaly, myalgia | Leukocytosis, anemia, increased ESR, CRP, liver enzymes & ferritin | Persistent pigmented plaques on trunk and limbs | Vascular and perivascular erosion on hands and feet | Methotrexate, Prednisone |
| Thien et al. [17] | 1/12/F | F | Fever, polyarthralgia, polyarthritis, myalgia | Leukocytosis, increased ESR & ferritin | Persistent pigmented plaques on trunk and limbs | Vascular and perivascular ulceration on head, trunk, buttocks, and shins | Methotrexate, Prednisone |

**Table 1**: Clinical manifestations and histopathological findings of Still’s disease
| Author/Year | No of patients/age (range) /Sex | Clinical presentation | Laboratory findings | Cutaneous manifestation | Skin Histology | Treatment |
|-------------|---------------------------------|-----------------------|---------------------|------------------------|----------------|-----------|
| Tomaru et al. [23] | 1/34/F | Fever, polyarthralgia, lymphadenopathy | Leukocytosis, increased CRP, liver enzymes & ferritin | Persistent pruritic erythematous papules with linear arrangement and pigmented changes on chest and back, evanescent salmon-pink eruption on lower extremities | Mild acanthosis, exocytosis, dyskeratotic cells and liquefaction degeneration in the basal layer, with lichenoid inflammatory reaction | Corticosteroids, Cyclosporine, Methotrexate |
| Criado et al. [31] | 1/52/F | Fever, polyarthralgia, sore throat, mild hepatomegaly, lymphadenopathy | Leukocytosis, increased ESR, CRP, & ferritin, hypergammaglobulinemia | Lenticular urticaria-like rash on face, thorax, abdomen, hands | Interstitial edema in reticular and papillar dermis with neutrophils and leukocytes around vasculitis-free vessels. | NSAIDs, Methotrexate, Thalidomide |
| Yang et al. [35] | 1/47/F | Fever, polyarthralgia, sore throat, myalgia, pleural effusion, splenomegaly | Leukocytosis, elevated liver enzymes & ferritin | Persistent violaceous scaly maculopapular rash with linear lesions on forehead, neck, elbows, knees | Necrotic keratinocytes in the upper epidermis and perivascular infiltrate of lymphocytes and neutrophils | Methyl-prednisolone, Azathioprine |
| Wolgamot et al. [39] | 1/55/F | Fever, polyarthralgia | Leukocytosis, increased ESR, CRP & ferritin | Pruritic maculopapular rash, plaques on face, extremities, trunk | Pattern with dyskeratotic keratinocytes in upper epidermis and stratum corneum | Prednisone, Methotrexate, Etanercept, Anakinra |
| Yanai et al. [41] | 1/43/M | Fever, arthralgia, myalgia, myositis | Increased fibrinogen CRP, creatine kinase & ferritin | Salmon-pink rash on upper arm | Perivascular lymphocytes infiltration and fragmentation of blood cells compatible with leukocytoclastic vasculitis | NSAIDs, corticosteroids |
| Fortna et al. [40] | 3/15-54/F | Fever, polyarthralgia, myalgia, sore throat | Leukocytosis, increased ESR, CRP, liver enzymes & ferritin | Pruritic erythematous blanchable papules and plaques on back, neck, abdomen, limbs | Hyperkeratosis with patchy parakeratosis, areas of dyskeratosis to upper layers of epidermis, and mild acanthosis. | Methyl-prednisolone, Methotrexate, Anakinra |
| Criado et al. [26] | 2/27-34/F, 1/26/M | Fever, arthritis, sore throat, lymphadenopathy, pleural effusion, splenomegaly | Leukocytosis, anemia, increased ESR, CRP & liver enzymes, hyperferritinemia | Urticarial pruritic rash, linear lesions (dermographism) on trunk, limbs, face | Perivascular and interstitial inflammatory cell infiltrate of lymphocytes and neutrophils with leukocytoclasis. | Prednisone, Chloroquine, Methotrexate, Mizoribine |
| Nagai et al. [34] | 18/16-60/F | Fever, arthralgia, sore throat, splenomegaly, lymphadenopathy | Leukocytosis, increased CRP, liver enzymes & ferritin | Evanescent salmon-pink maculopapular eruption, persistent papules and plaques with linear erythema similar to prurigo pigmentosa, edema of eyelids mimicking dermatomyositis | Parakeratosis and necrotic keratinocytes in epidermis, inflammatory infiltrates of lymphocytes in the papillary and mid-dermis | Corticosteroids, Methotrexate, Mizoribine, Cyclosporin, Cyclophosphamide |
| Author/Year | No of patients/age (range) /Sex | Clinical presentation | Laboratory findings | Cutaneous manifestation | Skin Histology | Treatment |
|------------|---------------------------------|------------------------|---------------------|------------------------|---------------|-----------|
| Lee et al. [14] 30/17-67/F 6/17-67/M | Fever, arthralgia, sore throat, splenomegaly, lymphadenopathy | Leukocytosis, elevated liver enzymes & ferritin | Evanescent rash, persistent pruritic urticarial, violaceous papules and plaques, dermatographism-like, prurigo pigmentosa-like and dermatomyositis-like eruption on trunk, neck, face, limbs | Normal epidermis with perivascular infiltrate of neutrophils, necrotic keratinocytes in upper epidermis. | NSAIDs, Corticosteroids, Methotrexate, Azathioprine |
| Yoshifuku et al. [16] | 1/27/F Fever, polyarthralgia, sore throat, hepatosplenomegaly lymphadenopathy | Leukocytosis, increased CRP, elevated liver enzymes & ferritin | Pruritic pigmented erythematous plaques and dark-reddish papules on abdomen and back | Mild hyperkeratosis, and presence of dyskeratotic keratinocytes in upper epidermis | Corticosteroids, Cyclosporin, |
| Said et al. [37] | 1/23/M Fever, sore throat, myopericarditis, arthralgia, hepatosplenomegaly | Leukocytosis, increased ESR &CRP, elevated ferritin, raised cardiac enzymes | Urticated and erythematous plaques and papules on the dorsum of right hand and fingers | Superficial and deep perivascular infiltrates of lymphocytes and neutrophils | Corticosteroids, NSAIDs, Azathioprine |
| Cho et al. [24] | 1/38/F Fever, polyarthralgia, sore throat hepatosplenomegaly lymphadenopathy | Leukocytosis, elevated liver enzymes & ferritin | Prurigo pigmentosa-like persistent papules and plaques on anterior chest, abdomen, back | Parakeratosis, and perivascular infiltrations of lymphocytes, eosinophils and neutrophils in upper dermis | Methyl-prednisolone, Methotrexate, Hydroxychloroquine |
| Sarkar et al. [19] | 1/36/M Fever, arthritis, hepatosplenomegaly hemophagocytic lymphohistiocytosis | Leukocytosis, anemia, increased ESR, CRP, liver enzymes & ferritin, hypoalbuminemia | Pigmented patches and plaques on chest, dermal and mucosal hyper-pigmentation | Multiple necrotic keratinocytes in aggregates in upper epidermis | Corticosteroids |
| Cossi et al. [38] | 1/35/M Fever, cough, dyspnea myopericarditis | Increased CRP, liver enzymes & ferritin hypergammaglobulinemia | Pruritic erythematous-edematous plaques on trunk, upper limbs | Epidermal spongiosis, dermal infiltrate of perivascular lymphocytes and histiocytes, intra-vascular CD15+ neutrophils | Methyl-prednisolone, Immunoglobulin IV Methotrexate |
Anakinra monotherapy or in combination with a DMARD, resistant AOSD [46]. Laskari et al. provided evidence that disease. Recently effective biologic agents including TNF-fasalazine and minocycline have been used to treat this rare methotrexate (MTX), cyclosporine, azathioprine, sul-
disease modifying anti-rheumatic drugs (DMARDs), anti-inflammatory drugs (NSAIDs), oral corticosteroids, could be either drug-related (i.e. antibiotics, Anakinra) or the interstitium. The eosinophilic cutaneous manifestation perivascular eosinophils not just in the dermis but also in case, the histopathology findings of the new persistent by eosinophils, histiocytes and lymphocytes [45]. In our papules and plaques in which skin biopsy revealed eosinophils in the upper and mid-dermis [36–39]. In urticarial lesions the histopathologic findings demonstrate an intense infiltrate of mature CD15+ neutrophils between the dermal collagen bundles. This clinicopathological entity has recently been described as neutrophilic urticarial dermatosis (NUD) [40]. Dyskeratosis and dermal mucinosis represent distinctive cutaneous lesions of AOSD [41, 42]. The presence of fibrin thrombi in the small vessel with scarce inflammatory cell infiltration, suggestive of vasculopathy [25] has also been observed in cases of AOSD. Leukocytoclastic cutaneous vasculitis [43, 44] with mixed cryoglobulinemia [44] in AOSD has been described only rare in the literature.

Eosinophils that are commonly seen in drug-induced eruption are consistently lacking in the AOSD-associated skin lesions [14]. Perez et al. described a case of AOSD-related persistent erythematous rash characterized by papules and plaques in which skin biopsy revealed perivascular infiltration of the small vessels in the dermis by eosinophils, histiocytes and lymphocytes [45]. In our case, the histopathology findings of the new persistent cutaneous eruption included the presence of several perivascular eosinophils not just in the dermis but also in the interstitium. The eosinophilic cutaneous manifestation could be either drug-related (i.e. antibiotics, Anakinra) or AOSD-associated.

Treatment of AOSD has been empirical. Non-steroidal anti-inflammatory drugs (NSAIDs), oral corticosteroids, disease modifying anti-rheumatic drugs (DMARDs), methotrexate (MTX), cyclosporine, azathioprine, sul-
fasalazine and minocycline have been used to treat this rare disease. Recently effective biologic agents including TNF-a, IL-1 and IL-6 antagonist have been used for steroid-resistant AOSD [46]. Laskari et al. provided evidence that Anakinra monotherapy or in combination with a DMARD, such as MTX may be the treatment of choice for patients with refractory Still’s disease [47]. MTX is recommended in patients with polyarthritis and allows for steroid dose sparing in AOSD [48]. Our patient did not respond to corticosteroid treatment, but showed dramatic response to initiation of Anakinra treatment.

In summary, AOSD can manifest with atypical skin lesions that have highly distinctive but non-pathognomonic pathological features and are usually associated with severe disease. Still’s rash can mimic various disorders with maculopapular, urticarial, linear and lichenoid manifestations and skin biopsy of those atypical cutaneous lesions is strongly recommended before or during the treatment course of AOSD because it allows rheumatologists and pathologists to recognize those specific distinctive histopathological characteristics and put the correct diagnosis.

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Compliance with ethical standards

Conflict of interest There is no conflict of interest. All authors participated in the preparation of this manuscript.

Human and animal rights For this case report formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in the study.

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