An atypical persistent eruption of adult-onset Still's disease with neutrophilic urticarial dermatosis-like dermal features: A case report and review of the literature

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder with unknown etiology. Cutaneous manifestations of AOSD could be typical (evanescent maculopapular rash, salmon-pink, and non- or mildly pruriginous) or atypical (persistent lesions with pruritus). In typical AOSD, microscopic assessment shows non-specific features such as very mild dermal inflammatory infiltrate (lymphocytes and neutrophils), and in atypical AOSD, it shows highly suggestive dyskeratotic/necrotic keratinocytes with neutrophilic and lymphocytic dermal infiltrate.[1–3] Neutrophilic urticarial dermatosis (NUD) is an autoinflammatory condition recently described as recurrent urticarial eruption vanishing within 24 hours with histologically marked neutrophilic infiltrate and leukocytoclasia. NUD is a rare cutaneous presentation of AOSD.[4] We report two cases of atypical persistent eruption of AOSD with dyskeratotic/necrotic keratinocytes and in one case leukocytoclasia (as an NUD-like dermal pattern) that has rarely been described previously. Knowledge of the clinico-pathological spectrum of atypical AOSD should facilitate diagnosis of this rare and severe disease.

1 | CASE 1

A 59-year-old Asian woman presented to the hospital with intermittent spiking fever (>39°C), polyarthralgia, sore throat, and weight loss, along with a recurrent and evanescent urticarial eruption over the last month. These symptoms were partially relieved by non-steroidal anti-inflammatory drugs. Dermatologic examination (Figure 1A-D) showed slightly hyperpigmented and disseminated erythematous pruriginous plaques predominating over the trunk, shoulders, back, and extensor surface of the limbs but sparing the face. Some lesions appeared urticarial, and others were scaly. A linear disposition suggested that the Koebner phenomenon was induced by scratching. Physical examination revealed axillary lymph node enlargement. Laboratory studies showed leukocytosis (15,470/mm^3 with 81% neutrophils and 2.7% eosinophils), anemia (hemoglobin 10.8 g/dL), high levels of serum ferritin (15,958 μg/L) with very low levels of glycosylated ferritin (<5%), an increased C-reactive protein (CRP) of 200 mg/L and slightly abnormal liver function tests (ASAT 128 U/I, ALAT 34 U/I, GGT 93 U/I, PA 131 UI/L). Antinuclear autoantibodies and rheumatoid factor assays were negative. There was no serological evidence for infection; Human immunodeficiency virus (HIV), Hepatitis A, B, C, E, Epstein-Barr virus (EBV), Cytomegalovirus (CMV), Human T-lymphotropic virus 1 (HTLV-1), Human T-lymphotropic virus 2 (HTLV-2), Human Herpesvirus 6 (HHV-6), *Treponema pallidum*, *Toxoplasma gondii*, *Rickettsia rickettsii*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Borrelia burgdorferi* studies were all negative. QuantiFERON-TB Gold in-Tube, blood cultures, thick blood smear, and cryoglobulinemia were also negative. Joint ultrasound confirmed polyarthritis and tenosynovitis. Heart ultrasound showed no signs of endocarditis or rheumatic disease. Thoracic and abdomen-pelvic CT scans showed axillary lymph node enlargement with no other abnormalities. Skin biopsy revealed hyperkeratotic epidermis with a mound of parakeratosis and numerous dyskeratotic/

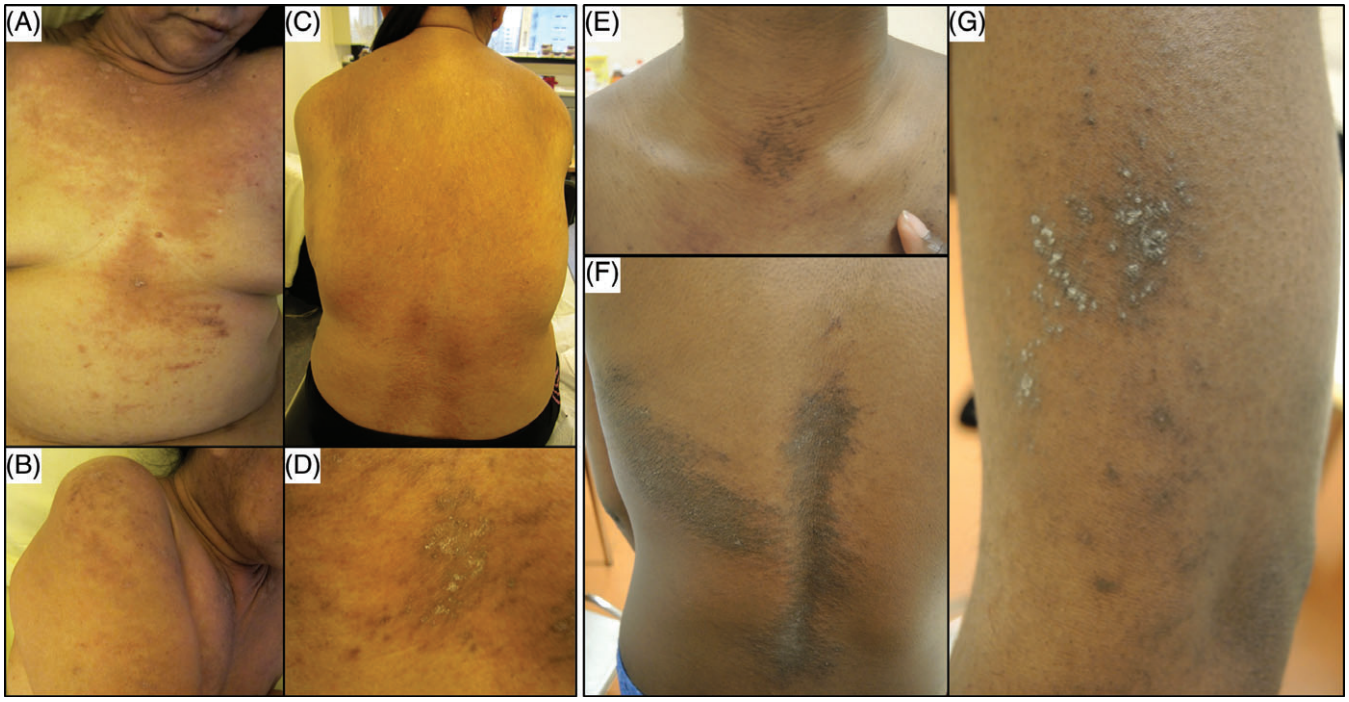

FIGURE 1 Case 1 clinical features: A, B, Slightly hyperpigmented and disseminated erythematous papules and plaques, predominating over the trunk, shoulders, back, and extension surface of the limbs; C, A linear disposition suggestive of Koebner phenomenon after scratching; D, Scaly and persistent lesions. Case 2 clinical features: E, F, Persistent hyperpigmented and disseminated papules and plaques, predominating over the neck, and back; G, Scaly and persistent lesions over the upper limbs

necrotic keratinocytes in the superficial layers. There was slight interface dermatitis. Superficial dermal perivascular and interstitial polymorphous inflammatory infiltrates with neutrophils, eosinophils, and leukocytoclasia were observed (Figure 2). No fibrinoid necrosis of vessels or prominent papillary edema was observed. The presence of leukocytoclasia in association with dyskeratotic/necrotic keratinocytes is exceptional in AOSD (Table 1) and is a characteristic feature of NUD. Diagnosis of atypical persistent eruption of AOSD was made because more than five of Yamaguchi's criteria were fulfilled, and infectious and autoimmune diseases were ruled out. Additionally, high levels

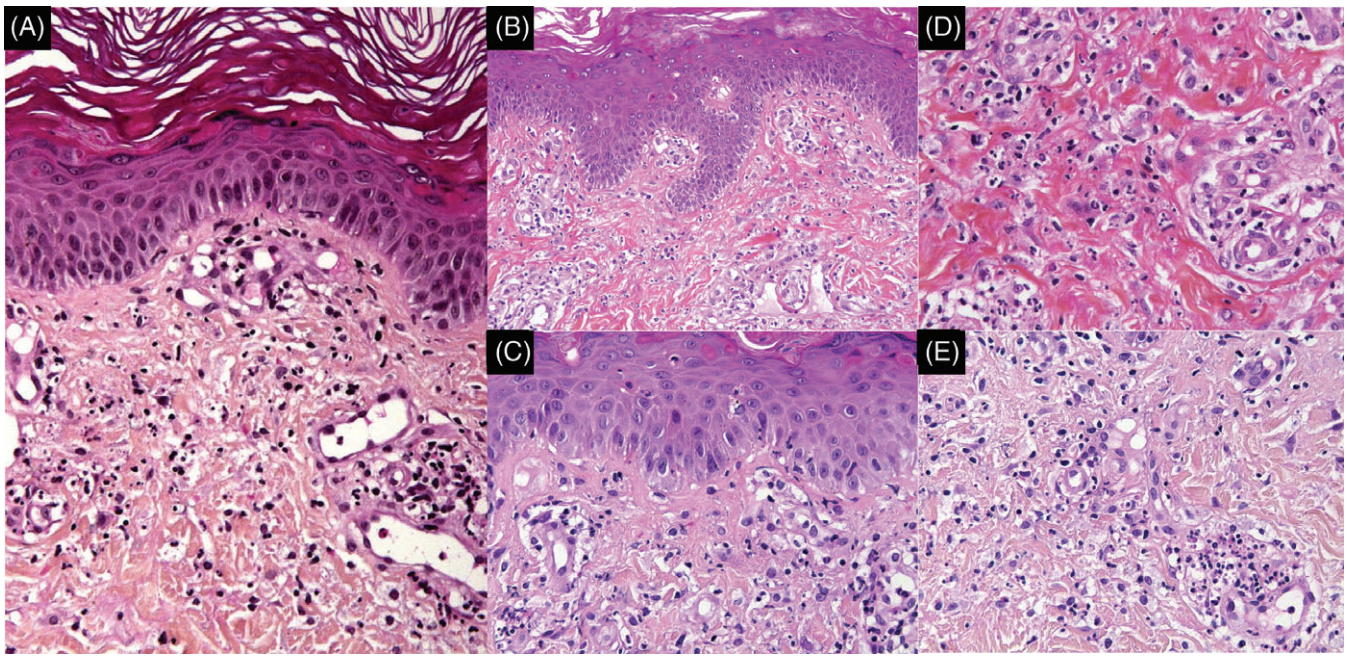

FIGURE 2 Case 1 microscopic features: A, characteristic hyperkeratosis with parakeratosis an dermal NUD-like pattern (neutrophils and numerous leukocytoclasia); B, Dyskeratotic/necrotic keratinocytes in superficial layers and superficial dermal mixed inflammatory infiltrate; C, Discrete interface dermatitis with basal apoptotic keratinocytes and vacuolization. Superficial epidermic layers displayed dyskeratotic/necrotic keratinocytes; D, Neutrophils with leukocytoclasia; E, Neutrophils with leukocytoclasia without frank vasculitis. Hematoxylin-Eosin-Saffron staining; ×100 (A), ×200 (B), ×400 (C-D-E) magnification. NUD, neutrophilic urticarial dermatosis

TABLE 1 Clinical and histopathological features of atypical cutaneous presentations of AOSD. Review of the literature

Age, gender, and ethnicity	Skin lesions morphology	Distribution	Histology		References
			Superficial dyskeratosis	Dermal infiltrate	
19, F, White, *n* = 1	Persistent papules and plaques	Trunk and arms, bilateral and symmetric	No	Perivascular and peri-appendageal lympho-mononuclear infiltrate	Kaur et al[5]
32, F, ENR, *n* = 1	Urticarial rash for less than 12 hours per day, Dermographism	Widespread	No	Neutrophilic urticaria	Setterfield et al[6]
16, F, White, *n* = 1	Persistent papules and plaques	Neck, forehead, and back	Yes	Mixed perivascular infiltrate	Lübbe et al[7]
55, F, ENR, *n* = 1	Mildly pruritic confluent urticarial rash	Trunk, limbs, face	No	Neutrophilic urticaria	Salaffi et al[8]
25, M, Asian, *n* = 1	Persistent papules and plaques	Trunk, chest, back	NA	NA	Suzuki et al[9]
39, M, White, *n* = 1	Persistent erythematous papules and plaques	Neck, trunk, limbs	No	Mixed perivascular infiltrate with scattered eosinophils	Perez et al[10]
43, 64, F, Asian, *n* = 2	Persistent generalized erythema	Face, limbs, and trunk	No	Moderate perivascular mononuclear cell infiltration few perivascular neutrophils	Fujii et al[11]
29, F, ENR, *n* = 1	Persistant erythematous plaques	Arms, dorsal hands, upper chest and back	Yes	Perivascular lymphocytic-interstitial eosinophilic infiltrate	Affleck et al[12]
19-67, 8F 3M, Asian, *n* = 11	Persistent papules	Widely distributed with photoaccentuation	Yes (*n* = 11)	Sparse to moderately dense mixed perivascular and interstitial infiltrate Occasionally: Nuclear dust	Lee et al[1]
23, F, Asian, *n* = 1	Persistent pigmented pruritic, macules, papules and plaques	Trunk, abdomen	No	Perivascular lympho-mononuclear infiltrate Scattered eosinophils	Thien Huong et al[13]
34, F, ENR, *n* = 1	Persistent prurigo pigmentosa-like papular eruption	Chest and upper aspect of the back	Yes	Mixed dense dermal infiltrate Interface dermatitis	Tomaru et al[14]
47, F, Asian, *n* = 1	Persistent papules	Forehead, neck, elbows, and knees	Yes	Superficial mixed perivascular infiltrate	Yang et al[15]
29, F, ENR, *n* = 1	Persistent papules	Neck and upper trunk	No	Mild mixed perivascular and interstitial infiltrate	Fernández-Guarino et al[16]
36, F, African-American, *n* = 1	Persistent pigmented eruption	Neck, trunk	No	Mixed perivascular infitrate with few eosinophils	Maza et al[17]
15, 54, 53, F, Asian, *n* = 3	Persistent pruritic papules and plaques	Proximal extremities, back, abdomen, ankles Upper back and chest linear pigmentation	Yes (*n* = 3)	Sparse superficial and mid-dermal mixed infiltrate	Fortna et al[18]
17-67, 30F 28M, Asian, *n* = 36	28 patients with persistent eruptions; urticarial, lichenoid, linear and dermatographism-like; dermatomyositis-like; prurigo pigmentosa-like; lichen-amyloidosis-like	Trunk, neck, face, extensor sides of the extremities Photoaccentuation	Yes (*n* = 28)	Mixed upper and mid dermis inflammatory infiltrate Occasionally: Nuclear dust without vasculitis	Lee et al[2]
38, F, ENR, *n* = 1	Prurigo pigmentosa-like persistent papules and plaques	Anterior chest wall, abdomen, and back	Yes	Mixed dermal perivascular infiltrate	Cho et al[19]
28-39, F, ENR, *n* = 5	Persistant papules and plaques	Widespread	Yes (*n* = 1)	Mixed inflammatory infiltrate in the upper dermis	Akkurt et al[20]
33-83, F, ENR, *n* = 6	Persistent pruritic papules and plaques	Back, chest, neck, extremities, face	Yes (*n* = 6)	Mild mononuclear perivascular infiltration (*n* = 2)	Kikuchi et al[21]

(*Continues*)

TABLE 1 (Continued)

Age, gender, and ethnicity	Skin lesions morphology	Distribution	Histology		References
			Superficial dyskeratosis	Dermal infiltrate	
19-35, F, Asian, Hispanic, *n* = 3	Persistent papules and plaques	Widespread	Yes (*n* = 1, one patient biopsied)	Superficial mixed dermal infiltrate	Sun et al[3]
56, F, Hispanic, *n* = 1	Erythematous and brown edematous plaques Linear and reticulated, lichenoid papules	Extensor forearms, neck, upper chest, lower extremities	Yes	Superficial mixed perivascular inflammatory infiltrate	Kavusi et al[22]
29-54-52, 2F 1M, 1 Caucasian, 2 Hispanic, *n* = 3	Persistent urticarial rash or persistent pruritic papules and plaques (flagellate erythema-type appearance) or persistent pruritic plaques and concomitant urticarial Evanescent rash	Trunk, limbs, Chest	Yes (*n* = 1)	Superficial perivascular Inflammatory cell infiltrate Perivascular inflammatory Infiltrate in the upper and Mid-dermis, without vasculitis	Narváez Garcia et al[23]
59, 28, 2F, Asian/ African, *n* = 2	Persistent slightly pigmented and disseminated erythematous plaques	Trunk, shoulders, back, and extensor surface of the limbs	Yes (*n* = 2)	NUD-like features (*n* = 1)	Present cases

Abbreviations: AOSD, adult-onset Still's disease; ENR, ethnicity not reported; F, Female; M, Male; NA, not available; NUD, neutrophilic urticarial dermatosis.

of serum ferritin (15,958 μg/L) with very low levels of glycosylated ferritin (<5%) were highly suggestive of this diagnosis.[24] Oral corticosteroid (1 mg/kg) treatment was started. It controlled the fever and arthralgia within 48 hours, as well as reduced CRP and ferritin levels and normalized liver function tests, but skin lesions persisted. Methotrexate (7.5 mg/week then 15 mg/week) was introduced 10 days later. Twenty days later, the oral corticosteroid was tapered. After 7 weeks, significant improvement was noted.

2 | CASE 2

A 28-year-old woman, HIV+, presented with pruritic and persistent skin eruption without an evanescent rash over the last 2 months. After 4 weeks, she developed a daily spiking fever (>39°C) and after 6 weeks, polyarthralgia. Symptoms were partially relieved by non-steroidal anti-inflammatory drugs and acetaminophen. Dermatologic examination (Figure 1E-G) showed hyperpigmented and disseminated plaques predominating over the upper limbs, trunk, shoulders, and back. Some lesions appeared scaly. Joints were swollen and tender. Laboratory studies showed neutrophilic leukocytosis (12,240/mm^3), microcytic anemia, high levels of serum ferritin (2592 μg/L), an increased CRP of 123 mg/L and slightly abnormal liver function tests. Serum antinuclear autoantibodies were positive (1/160), and rheumatoid factor assay was negative. No serological evidence for recent or active infections was observed; Hepatitis B, C, EBV, CMV, *T. pallidum*, *T. gondii*, *M. pneumoniae*, *C. pneumoniae*, and *B. burgdorferi* studies were all negative. Skin biopsy (Figure 3) showed mounds of hyperkeratosis with parakeratosis and numerous dyskeratotic cells mainly in the superficial layers. Superficial to mid dermal perivascular and minimally interstitial mononuclear cell infiltration was observed with a few neutrophils and without leukocytoclasia.

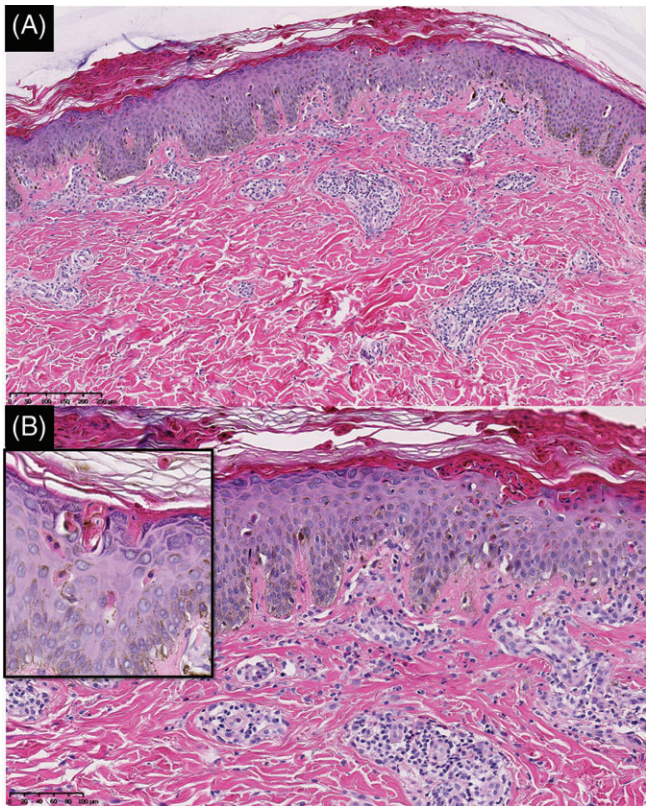

FIGURE 3 Case 2 microscopic features: A, B, Mounds of hyperkeratosis with parakeratosis and numerous dyskeratotic cells (in frame) mainly in the superficial layers and superficial to mid dermal perivascular and minimally interstitial mononuclear cell infiltration with a few neutrophils and without leukocytoclasia. Hematoxylin-Eosin staining; ×40 (A), ×200 (B) ×400 (in frame) magnification

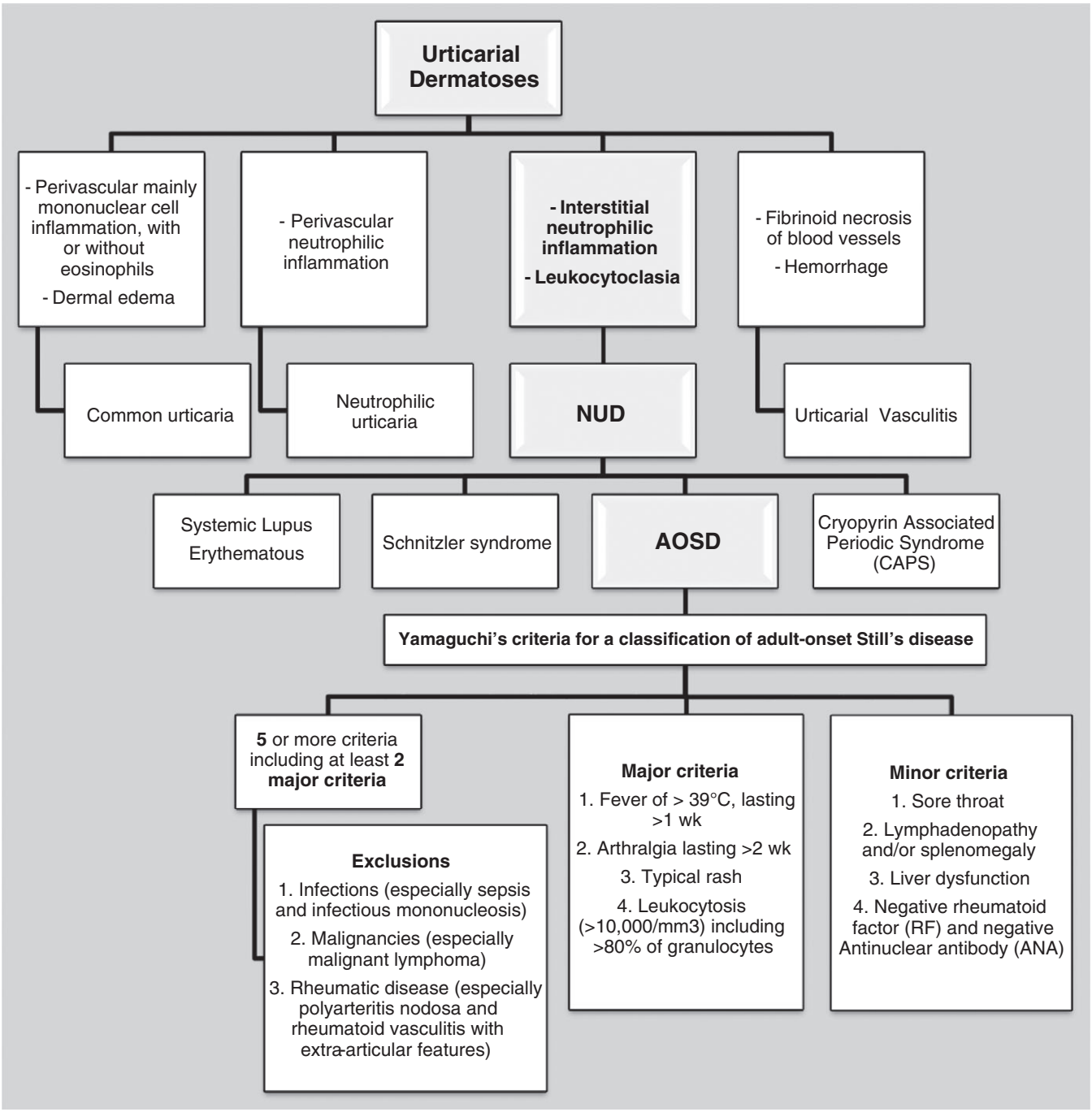

FIGURE 4 Histopathological diagnosis of urticarial dermatoses and clinical correlates of NUD and AOSD with Yamaguchi's criteria. NUD, neutrophilic urticarial dermatosis; AOSD, adult-onset Still's disease

No fibrinoid necrosis of vessels or prominent papillary edema was observed. Diagnosis of atypical persistent eruption of AOSD was made. Oral corticosteroid (6 mg/day) treatment was started. It controlled the fever, but arthralgia and skin lesions persisted. Ledertrexate (6 mg/week) and intravenous corticosteroid (1 g/2 weeks) were introduced. After 3 months, significant improvement was noted.

3 | DISCUSSION

AOSD displays large clinical heterogeneity. It is often an exclusion diagnosis, and infectious, autoimmune, and neoplastic diseases should be ruled out. Because of the lack of specific tests, this entity can be misdiagnosed and inadequately treated. Its main clinical features are a spiking fever, polyarthralgia, salmon-colored maculopapular rash, sore throat, lymphadenopathy, and hepatosplenomegaly. Serological abnormalities include mainly leukocytosis, elevated granulocyte counts, and abnormal liver function tests. These clinical and serological features are referred to as the standard Yamaguchi's criteria.[24] With 5 or more Yamaguchi's criteria, including 2 or more major criteria, a sensitivity of 96.2%, and a specificity of 92.1% are reached. In 1996, Masson et al[25] compared criteria in AOSD; Yamaguchi's criteria were the most sensitive (93.5%), followed by Cush's (80.6%) and Calabro's (80.6%). Additionally, Fautrel et al.[24] proposed

low glycosylated ferritin fraction as a specific marker of AOSD, with a sensitivity of 43.2% and a specificity of 92.9%. They compared Fautrel classification and Yamaguchi's criteria; the specificity of the Yamaguchi's criteria remained higher in this study. AOSD cutaneous manifestations can be classified as typical evanescent rashes or atypical persistent eruptions. Herein, we report two cases with atypical persistent AOSD eruptions and characteristic necrotic keratinocytes; one case had an NUD-like dermal pattern with leukocytoclasia on histopathological examination. Prior reports of atypical persistent AOSD have described persistent plaques and/or papule that were often pruriginous, less frequently erythematous, urticarial, flat-topped, dusky red or brownish, scaly or crusted, linear urticarial or lichenoid (Table 1).[1–3,5–23]

In these atypical cutaneous features, the main dermal feature was an inflammatory infiltrate; with variable intensity, the dermal feature was more often perivascular than interstitial, with lymphocytes and neutrophils. Frank vasculitis was never noticed. The second histological hallmark, dyskeratotic/necrotic keratinocytes typically found in superficial layers, suggests that a skin biopsy is recommended (Table 1). Only Lee et al[2] reported minimal leukocytoclasia. More recently, in 2014, Cozzi et al[26] reviewed 21 publications of AOSD with cutaneous involvement, 7 reported atypical cutaneous without leukocytoclasia.

The review of these publications highlights the atypical histological presentation of our case with NUD-like dermal features as a neutrophilic infiltrate with leukocytoclasia. First, it is important to recognize NUD because it is associated with systemic diseases and autoimmune or autoinflammatory conditions such as systemic lupus erythematosus, Schnitzler syndrome, and cryopyrin-associated periodic syndrome (Figure 4).[24,27]

Second, Sun et al[3] reported malignant tumors (mainly lymphoma and breast cancers) after the diagnosis of atypical AOSD and suggested close follow-up in a patient in whom symptoms seem difficult to control. Clinical complications including serositis, myopericarditis, lung and neurologic involvement, abdominal pain, and reactive hemophagocytic syndrome have also been reported in persistent and severe atypical AOSD with an 8% mortality rate.[23] Moreover, recognizing leukocytoclasia in AOSD allows efficient treatment with interleukin 1 receptor antagonist (anakinra) in AOSD with NUD-features.[28]

In conclusion, because atypical persistent eruption in AOSD is rare with variable clinicopathologic presentations, diagnosis can be challenging. Herein, we report unusual NUD-like dermal changes in atypical AOSD. We believe that dermatopathologists should recognize NUD features in AOSD to make an earlier diagnosis and permit adequate treatment.

Conflict of interest

The authors declare no potential conflict of interests.

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