Erythroderma and persistent erythema in adult-onset Still disease associated with macrophage activation syndrome

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Key words: adult-onset Still disease; hemophagocytic lymphohistiocytosis; juvenile idiopathic arthritis; macrophage activation syndrome.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) and its related disorder, macrophage activation syndrome (MAS), are rare life-threatening syndromes of immune hyperactivation precipitated by an array of triggers including autoimmune conditions, infections, genetic anomalies, and malignancy. Specifically, HLH and MAS may be associated with autoimmune connective tissue disorders such as juvenile idiopathic arthritis (JIA) and adult-onset Still disease (AOSD).[1,2] Adult-onset Still disease is an autoinflammatory condition that classically presents with spiking fevers, arthralgia, and an evanescent salmon-pink cutaneous eruption.[1] The cutaneous findings of AOSD can be classified as a typical evanescent rash or as an atypical presentation.[1] Atypical cutaneous presentations, most commonly persistent papules and plaques, are associated with an increased incidence of critical complications such as HLH/MAS.[1-3] We present the case of a critically ill patient with a history of JIA with new-onset erythroderma followed by persistent erythematous papules and plaques.

Abbreviations used:

AOSD:	adult-onset Still disease
HLH:	hemophagocytic lymphohistiocytosis
JIA:	juvenile idiopathic arthritis
MAS:	macrophage activation syndrome

CASE REPORT

A 32-year-old man with a past medical history significant for seizure disorder, type 1 pulmonary hypertension, and JIA presented to the emergency department with fever, malaise, dyspnea, and lower extremity edema. He was admitted to the intensive care unit with multiorgan failure. Based on the presence of splenomegaly, fever (39.8 °C), immunosuppressed state, cytopenias in more than 2 cell lineages, elevated ferritin (8,630 ng/mL; reference range, 24-366 ng/mL), hypofibrinogenemia, and transaminitis, the patient was diagnosed with MAS/HLH. Over the course of a month he was treated with tapering doses of anakinra and intravenous dexamethasone. He was stabilized and decannulated but remained in the intensive care unit for continued monitoring. The patient's hospital course was complicated by osteomyelitis, multilimb ischemia, and gangrene requiring digital and limb amputations. Prednisone was tapered to 10 mg daily, and the anakinra was discontinued. Subsequently, he developed erythroderma. Physical examination revealed erythematous papules and macules coalescing into generalized erythroderma of the face, neck, trunk, and proximal extremities (Fig 1). Punch biopsy demonstrated dyskeratosis and neutrophilic spongiosis (Fig 2). At this time, the patient had worsening respiratory status, renal function, pancytopenia, and elevated ferritin levels. Clinical and histopathologic correlation led to the diagnosis of AOSD. The patient's systemic corticosteroid dose was increased, and he was resumed on anakinra 100 mg daily. His erythroderma improved but his

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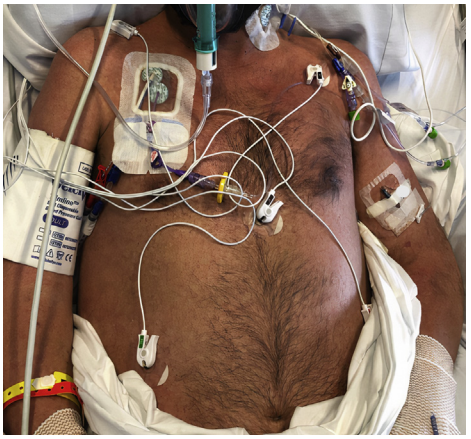

Fig 1. Erythematous papules and macules coalescing into generalized erythroderma of the face, neck, trunk, and proximal aspect of the extremities.

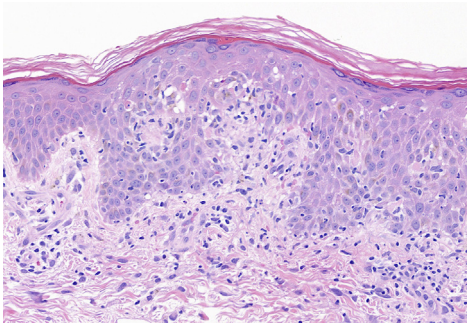

Fig 2. Neutrophilic spongiosis and dyskeratosis. (Hematoxylin-eosin stain; original magnification: ×200.)

underlying erythema and erythematous papules and plaques on his trunk and proximal extremities persisted (Fig 3). Due to relapse following discontinuation of anakinra and following corticosteroid taper, the patient was started on intravenous tocilizumab (2 total doses) and prednisone 80 mg daily with taper. His clinical symptoms and erythroderma again improved. He was diagnosed with persistent papules and plaques of Still disease, a rare cutaneous manifestation of AOSD. At the time of discharge, his neutropenia had improved with filgrastim and intravenous immune globulin, his pulmonary hypertension was controlled with treprostinil, and he was placed on an extended prednisone taper. He was discharged in stable condition.

DISCUSSION

Due to the absence of the typical evanescent cutaneous manifestations of AOSD, the early presentation of erythroderma in this severely ill patient was initially favored to represent a drug hypersensitivity eruption. However, the clinical history,

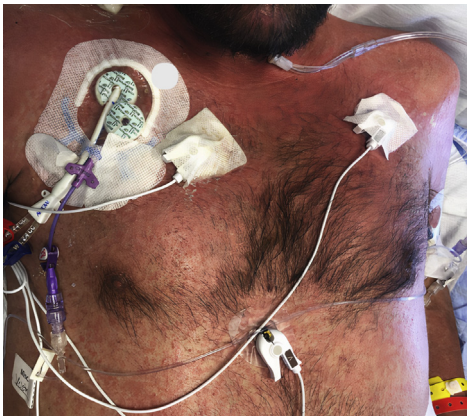

Fig 3. Persistent erythematous papules and plaques on the trunk and proximal aspect of the extremities.

histopathologic features, and repeated dramatic response to antiinterleukin 1 therapy led to the diagnosis of AOSD with atypical cutaneous manifestations. Prompt therapy for AOSD is essential, but timely diagnosis can be challenging in the setting of atypical clinical presentations. A systematic review found that 75% of atypical presentations included persistent papules and plaques, as seen in our patient.[1] The primary lesions of AOSD can vary in color and may have a violaceous hue.[1] Additionally, 7% of patients with atypical presentations were found to have persistent erythema, as demonstrated in the patient described.[1]

Both JIA and AOSD revolve around innate immune pathways with key cytokines such as interleukin 1 and interleukin 18.[3] HLH in the setting of an autoimmune disorder is termed MAS, and these 2 disorders occur on a spectrum.[3] Patients with JIA or AOSD—particularly those with atypical cutaneous manifestations—are at increased risk of HLH/MAS.[1-3] One criterion used for diagnosing adult HLH or MAS is the HScore. The HScore reflects fever, hepatosplenomegaly, immunosuppression, cytopenia in >2 cell lines, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, elevated liver function tests, and presence of hemophagocytosis; a score of >169 is 93% sensitive and 86% specific for HLH/MAS.[3,4] For the patient described here, the HScore was 194. Ferritin is key for the diagnosis with levels <500 unlikely to be MAS and >10,000 suggestive of probable MAS.[3] Multiple organs can be affected in MAS, and patients can present with multiorgan failure, as in this case.[2,3] Up to 58.2% of patients with MAS require mechanical ventilation, and up to 53.6% require inotropic support.[2] Overall mortality in adults with MAS associated with autoimmune disease ranges from 5% to 39%, making timely diagnosis and treatment imperative.[3]

Table I. A comparison of typical and atypical adult-onset Still disease

Features	Typical AOSD	Atypical AOSD
Historical	Cutaneous eruptions occur after fever in the setting of other systemic symptoms[1,5] Viral and bacterial infections have been codiagnosed, suggesting a triggering effect[5]	Cutaneous eruptions occur concurrently with classic symptoms of AOSD or shortly afterwards. Rarely, atypical findings occur at presentation[1]
Demographic	Women (increased risk during second trimester of pregnancy and postpartum); young adults (median, 36 y of age)[5]	Women, East-Asian descent, 18-83 y of age[1]
Clinical	Intermittent high spiking fevers, arthralgias/arthritis (wrists, knees, ankles), typical evanescent rash, sore throat, generalized lymphadenopathy, transaminitis, and splenomegaly[1,5]	Persistent papules and/or plaques (75%) that are pruritic and brown to violaceous in color with crusting. Lesions are most commonly located on the trunk and extensor surfaces.[1] Other presentations: urticarial papules, lichenoid papules, pigmented plaques, dermatomyositis-like, lichen amyloidosis-like, and prurigo pigmentosa-like[1] Typical clinical symptoms plus lymphadenopathy, hepatosplenomegaly, transaminitis, serositis, myopericarditis, lung involvement, abdominal pain, and neurologic involvement[1]
Laboratory	Leukocytosis, neutrophilia, and hyperferritinemia (5 times the normal value) with a glycosylated ferritin level <20%.[1,5] Elevated levels of ESR and CRP, anemia, and thrombocytosis[5]	Hyperferritinemia, specifically enriched H-ferritin in biopsies from persistent AOSD, along with typical laboratory findings[1]
Pathology	Nonspecific interstitial inflammation has been demonstrated in the myocardium, lung, liver, and GI tract.[5] Hepatic necrosis and nonspecific "reactive inflammatory bone marrow" may also be present[5]	Biopsies with increased $CD68^{+}$/H-ferritin $^{+}$ cells[1] Persistent papules and plaques or generalized erythema: single or aggregated dyskeratotic/necrotic keratinocytes in the upper portion of the epidermis with perivascular lymphocytes and neutrophils[1] Urticarial: papillary dermal edema with perivascular and interstitial neutrophilic infiltrate[1]

AOSD, Adult-onset Still disease; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *GI*, gastrointestinal.

Recognition of atypical cutaneous manifestations of AOSD (Table I) may enable dermatologists to aid in the diagnosis of the rare, but associated, critical complication of HLH/MAS.[5] Early recognition of an otherwise difficult diagnosis may potentially decrease morbidity and mortality in critically ill patients.

Conflicts of interest

None disclosed.

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