Received: 2 March 2023 | Revised: 22 March 2023 | Accepted: 24 March 2023

DOI: 10.1002/ccr3.7181

CASE REPORT

Clinical Case Reports Open Access WILEY

Cutaneous granuloma annulare in an adult patient with macrophage activation syndrome

Ruixin Deng[1,2,3,4] | **Xingye Meng**[1,2,3,4] | **Aiping Wang**[1,2,3,4] | **Ruoyu Li**[1,2,3,4]

[1]Department of Dermatology and Venerology, Peking University First Hospital, Beijing, China

[2]National Clinical Research Center for Skin and Immune Diseases, Beijing, China

[3]Research Center for Medical Mycology, Peking University, Beijing, China

[4]Beijing Key Laboratory of Molecular Diagnosis on Dermatoses, Beijing, China

Correspondence
Ruoyu Li, Department of Dermatology and Venerology, Peking University First Hospital, 8 Xishiku Street, Beijing, China.
Email: ruoyuli_myco@163.com

Abstract

Macrophage activation syndrome (MAS) is a rare but life-threatening disorder that is associated with multiple organ involvement. Here, we described cutaneous granuloma annulare in MAS. This novel histological finding is a reminder to explore the underlying mechanisms of skin involvement in MAS, which may reveal its pathogenesis.

KEYWORDS

allergy and immunology, dermatology, hematology

1 | INTRODUCTION

Macrophage activation syndrome (MAS) is a rare but life-threatening disorder that is associated with multiple organ involvement. Here, we described cutaneous granuloma annulare in MAS. This novel histological finding is a reminder to explore the underlying mechanisms of skin involvement in MAS, which may reveal its pathogenesis.

Hemophagocytic lymphohistiocytosis (HLH) is a condition of excessive immune activation that is both severe and potentially fatal.[1] Familial HLH (fHLH) and secondary or acquired HLH (sHLH) are the two recognized types of HLH.[2] When sHLH occurs in the context of autoimmunity, it is also called macrophage activation syndrome (MAS).[3] While MAS is most common in newborns under 18 months of age,[4] it has been reported in people of all ages.

MAS often manifests as a febrile illness with widespread organ involvement. Common symptoms include splenomegaly, hepatomegaly, lymphadenopathy, cytopenia, hyperferritinemia, and hypertriglyceridemia. Other clinical (such as disorientation, convulsions, and skin rash) or biochemical (such as a low fibrinogen level) abnormalities may also be detected, but they are less common. Previous studies summarized that more than one quarter of adult patients had cutaneous involvement.[5–8] Generalized rashes, erythroderma, edema, petechiae, and purpura are some of the cutaneous symptoms that might occur, and skin biopsy results are often nonspecific.[5] Histologically, this condition is characterized by lymphohistiocytic perivascular infiltrates in the reticular dermis, the absence of epidermal alterations, and the presence or absence of vasculitis.[6] Here, we describe a case of adult MAS with a novel skin histological feature of granuloma annulare (GA).

2 | CASE HISTORY

(7 September, 2022) A 52-year-old man was taken to the hospital after he complained of myalgia, itchy skin rashes, and intermittent fever (maximum temperature 39.0°C) for 2 weeks. He had no underlying diseases and no relevant family history. Physical examination found generalized red patches with desquamation on the forehead, chest, lumbosacral region, forearms, back of hands, and lower limbs, the color of which faded when pressed (Figure 1). Multiple enlarged tough lymph nodes were found in the supraclavicular region, posterior neck, bilateral axilla, and bilateral groin, with moderate motion and no tenderness. Physicians also found muscle tenderness proximal to the extremities, but muscle strength was normal. The following laboratory test results were found: complete blood count, 7.60×10^3/μL; hemoglobin, 1076 U/L; alanine aminotransferase (ALT), 11.8 g/dL; platelets, 1691 U/L; lactate dehydrogenase (LDH), 201×10^3/μL; aspartate aminotransferase (AST), 844 U/L; triglycerides (TGs), 3.7 mmol/L; ferritin (FER), 21,569 ng/mL; natural killer (NK) cell activity, 10.94%; soluble CD25 (sCD25), 2980 U/mL; and fibrinogen, 3.45 g/L. A mild degree of splenomegaly was observed by ultrasonography of the abdomen. GA (small clusters of histocytes, partially organized in a palisaded pattern) and lymphocytic perivascular infiltration in the superficial dermis were found by skin biopsy (Figure 2). Bone marrow aspiration revealed hemophagocytosis.

2.1 | Differential diagnosis and investigations

Diagnosis of MAS requires the exclusion of other systemic diseases, such as infection, tumor, and other autoimmune diseases.[5] Therefore, the patient underwent a series of examinations during hospitalization to obtain a comprehensive and accurate diagnosis. Various infection-related tests, including cytomegalovirus (CMV) and Epstein–Barr virus (EBV) examinations, were performed to rule out infectious diseases. The results of autoantibody spectrum testing were also negative. Since the patient had myalgia, dermatomyositis was considered carefully since

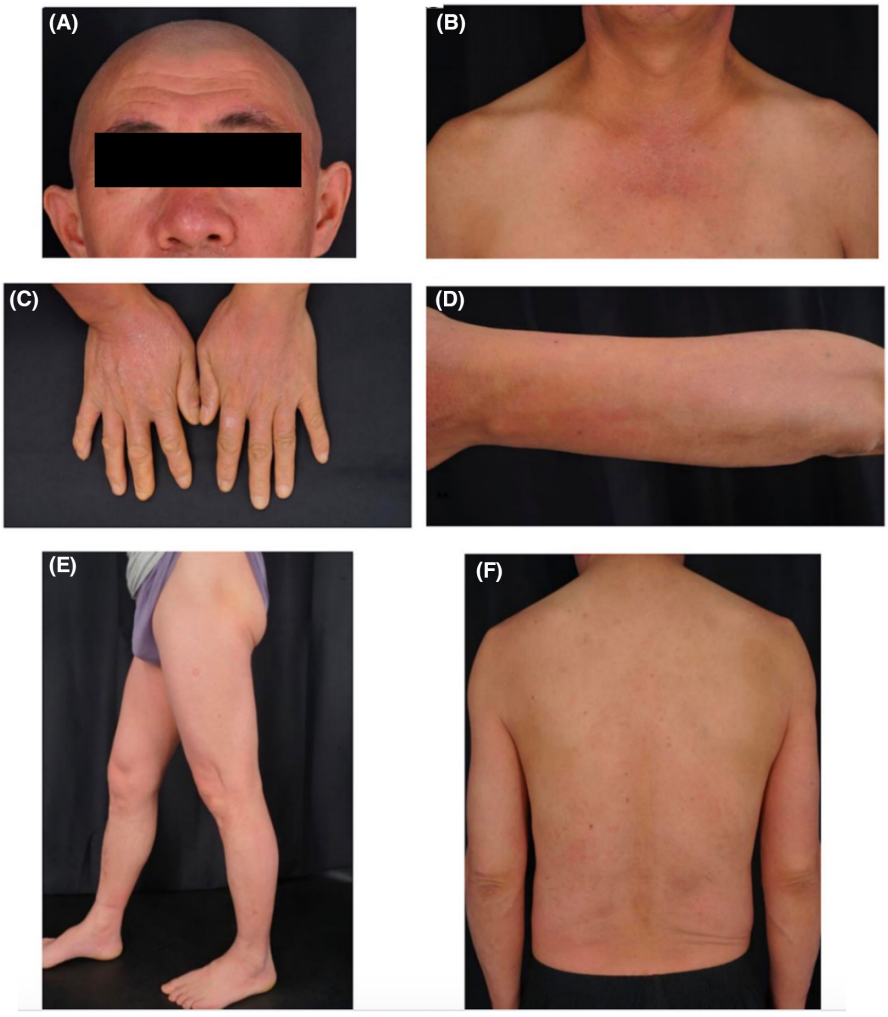

FIGURE 1 Red patches with desquamation on the forehead (A), chest (B), back of hands (C), forearm (D), lower limbs (E), and lumbosacral region (F).

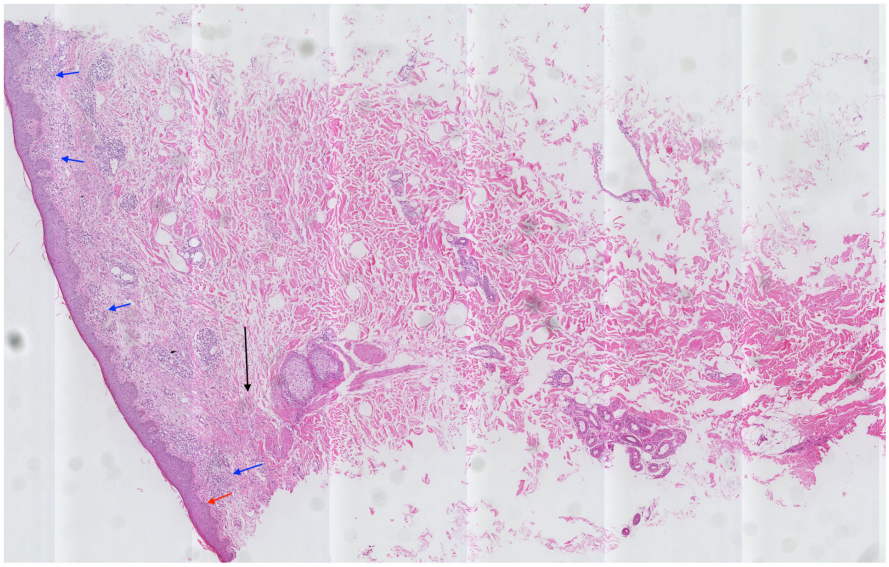

FIGURE 2 Skin biopsy specimen demonstrating basal cell edema in the epidermis (red arrow), lichenoid and perivascular focal lymphocyte infiltration in the superficial dermis (blue arrows), and granuloma annulare (small clusters of histocytes partially organized in a palisaded pattern, as the black arrow shows) in the superficial dermis.

it could also cause MAS-like symptoms. Therefore, various investigations, including myositis antibody spectrum tests, electromyography (EMG), and magnetic resonance imaging (MRI) of both legs, were conducted, which all demonstrated no muscle involvement. In addition, no malignancy was observed on positron emission tomography–computed tomography (PET-CT) or colonoscopy.

2.2 | Treatment and outcome

The patient first received glucocorticoids (methylprednisolone 48 mg daily for 3 days followed by dexamethasone 15 mg per day for 2 weeks) as initial treatment. Then, etoposide and ruxolitinib were administered as maintenance therapy. Specifically, the etoposide dosage was 50 mg twice a week for 2 weeks, was reduced to 50 mg once a week starting on October 14, 2022, and then was finally discontinued after 6 weeks. Ruxolitinib 10 mg twice a day was administered for nearly 4 months until January 18, 2023 (see Figure S1). The total follow-up time was 6 months after hospital discharge, during which detailed medical examinations were conducted every 2 weeks and no side effects were noted. A gradual return to normal in ALT/AST, TG, and FER levels occurred. All cutaneous symptoms disappeared, and the patient recovered well with no evidence of recurrence at the last follow-up.

3 | DISCUSSION

Clinically, MAS has characteristics that are similar to and may be mistaken for other systemic diseases and conditions, such as sepsis, cancer, and autoimmune diseases.[5] The requirements for a MAS diagnosis can be met only when a certain set of clinical characteristics are present. Unfortunately, there is no consensus to date on the diagnostic criteria for adult sHLH. The HLH-2004 criteria and HScore are currently in use.[9,10] When compared to the HLH-2004 criteria, Debaugnies et al.[11] showed that the HScore was more sensitive, with lower but still appropriate specificity. Our patient had a fever of 39.0°C, splenomegaly, hypertriglyceridemia, FER greater than 500 μg/L, sCD25 greater than 2400 U/mL, and hemophagocytosis in bone marrow, which met five of the HLH-2004 criteria, and he was thus diagnosed with MAS. It was also necessary to distinguish whether the clinical picture is due to other systemic diseases or conditions, such as infection, rheumatic diseases, or neoplastic diseases.[5] The patient underwent several examinations during hospitalization, all of which showed insufficient evidence of other systemic illnesses.

According to reports, 6%–65% of MAS patients have cutaneous eruptions.[6] Descriptions of the morphological characteristics, shape, and spread of these eruptions as nonspecific transitory rashes were previously common.[6] Currently, there are three main categories of cutaneous manifestations due to the increasing number of cases that have been reported[8]: (i) those that are specific to the underlying diseases (i.e., cutaneous lymphoma or systemic disease); (ii) those that reflect the biological effects of sHLH (i.e., thrombopenic purpura); and (iii) a generalized, transient, maculopapular rash that is typically nonspecific. In our study, the patient had generalized congestive plaques with desquamation, which belonged to the last type. To further clarify the nature of the cutaneous lesions, the patient underwent skin biopsy. Typical skin histology mostly exhibited perivascular infiltration of lymphohistiocytes in the reticular dermis. Lymphocytic infiltration of the superficial

dermis and hypodermis, as well as interface dermatitis, could also be observed.[8] The patient in our study had perivascular lymphocytic infiltration in the upper dermis, which was in accordance with a previous case report.[8] However, the skin biopsy specimen of this patient also revealed GA, which had not been observed in the cutaneous histopathology of MAS before. GA is characterized by focal collagen degeneration, inflammation with interstitial histiocytes, and mucin deposition.[12] As an occasionally histopathological mimic of GA, necrobiosis lipoidica (NL) should be carefully differentiated when diagnosing GA.[13] According to previous reports, differential diagnosis can be made based on the epidemiology, clinical manifestations, and histological findings by hematoxylin–eosin (HE) staining and mucin staining.[12–14] The patient in our report had no underlying diseases, and his skin lesions were generalized red patches with the histological feature of palisaded granuloma focally distributed in the upper dermis, none of which were consistent with NL. Therefore, we were able to exclude NL when diagnosing GA, although we did not perform mucin staining. Some researchers suggest that the connective tissue deterioration that characterizes GA may be traced back to a T helper type 1 (Th1) response involving interferon gamma (IFN-γ), which stimulates macrophages to produce matrix metalloproteinases.[12] Interestingly, this hypothesis is consistent with the current understanding of the pathophysiology of HLH. In HLH, enhanced IFN-γ-dependent stimulation has also been postulated as a causal mechanism of the uncontrolled activation of antigen-presenting cells (macrophages and histiocytes) and T cells.[15] Tissue damage and gradual systemic organ failure are both attributed in part to this activation, which may have a pathogenic role in the development of the primary clinical and laboratory characteristics of HLH.[16] Therefore, further research should be performed to explore the underlying mechanisms of cutaneous involvement in adult MAS, which may reveal more about the pathogenesis of MAS and thus help to improve the diagnosis and treatment of MAS.

MAS is a disease with a high risk of death and rapid progression.[6] Regardless of the etiology of MAS, initial treatment often involves glucocorticoids. In addition, a key therapeutic approach that may improve survival includes chemotherapeutic drugs such as etoposide.[5] Additionally, since IFN-γ is crucial in the development of MAS, Janus kinase (JAK) inhibitors are a potentially useful treatment strategy.[17] Ruxolitinib, a JAK1/2 inhibitor, has demonstrated remarkable activity in hyperinflammatory, cytokine-governed diseases. A two-month overall survival rate of 100% was observed in a pilot study of ruxolitinib in the treatment of patients with sHLH, and the drug was shown to be active and well tolerated.[17] Our patient responded well to the therapeutic approaches, and he showed no signs of recurrence throughout the follow-up period. To further assess the efficacy and safety of ruxolitinib and other JAK and signal transducer and activation of transcription (STAT) pathway inhibitors in patients with MAS, future prospective multicenter trials should be conducted.

There are some limitations in our study. First, we did not perform immunohistochemical staining of the skin specimen; thus, we could not obtain the specific cell subsets in GA. In addition, we did not perform genetic tests for the patient or his family members, although no family history was found.

In conclusion, we report a case of adult MAS with a novel cutaneous histological finding. Histological characteristics of skin lesions may indicate the underlying pathophysiology of MAS and might help clinicians, especially dermatologists, obtain a preliminary diagnosis of MAS. More research on the etiologies of cutaneous involvement and its correlation with the pathogenesis of MAS should be conducted in the future to promote MAS diagnosis and treatment and to bring a brighter future for MAS patients.

AUTHOR CONTRIBUTIONS

Ruixin Deng: Conceptualization; data curation; writing – original draft. **Xingye Meng:** Data curation; writing – original draft. **Aiping Wang:** Supervision; writing – review and editing. **Ruoyu Li:** Conceptualization; supervision; validation; writing – review and editing.

ACKNOWLEDGMENTS

Not applicable.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

ETHICAL APPROVAL

The study was approved by the Ethics Committee of Peking University First Hospital and was in compliance with the Declaration of Helsinki.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

ORCID

Ruixin Deng https://orcid.org/0000-0002-1570-7207

REFERENCES

1. Carter SJ, Tattersall RS, Ramanan AV. Macrophage activation syndrome in adults: recent advances in pathophysiology, diagnosis and treatment. *Rheumatology (Oxford)*. 2019;58(1):5-17. doi:10.1093/rheumatology/key006
2. Weitzman S. Approach to hemophagocytic syndromes. *Hematology Am Soc Hematol Educ Program*. 2011;2011:178-183. doi:10.1182/asheducation-2011.1.178
3. Henter JI, Elinder G, Söder O, Ost A. Histiocytosis syndromes in children. *Lancet*. 1987;1(8541):1091-1092. doi:10.1016/s0140-6736(87)90518-6
4. Ravelli A, Minoia F, Davì S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European league against rheumatism/American college of rheumatology/paediatric rheumatology international trials organisation collaborative initiative. *Arthritis Rheumatol*. 2016;68(3):566-576. doi:10.1002/art.39332
5. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet*. 2014;383(9927):1503-1516. doi:10.1016/s0140-6736(13)61048-x
6. Morrell DS, Pepping MA, Scott JP, Esterly NB, Drolet BA. Cutaneous manifestations of hemophagocytic lymphohistiocytosis. *Arch Dermatol*. 2002;138(9):1208-1212. doi:10.1001/archderm.138.9.1208
7. Millsop JW, Ho B, Kiuru M, Fung MA, Sharon VR. Cutaneous Hemophagocytic Lymphohistiocytosis: bean bags from the bone. *JAMA Dermatol*. 2016;152(8):950-952. doi:10.1001/jamadermatol.2016.0978
8. Fardet L, Galicier L, Vignon-Pennamen MD, et al. Frequency, clinical features and prognosis of cutaneous manifestations in adult patients with reactive haemophagocytic syndrome. *Br J Dermatol*. 2010;162(3):547-553. doi:10.1111/j.1365-2133.2009.09549.x
9. Fardet L, Galicier L, Lambotte O, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol*. 2014;66(9):2613-2620. doi:10.1002/art.38690
10. Henter JI, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48(2):124-131. doi:10.1002/pbc.21039
11. Debaugnies F, Mahadeb B, Ferster A, et al. Performances of the H-score for diagnosis of hemophagocytic lymphohistiocytosis in adult and pediatric patients. *Am J Clin Pathol*. 2016;145(6):862-870. doi:10.1093/ajcp/aqw076
12. Schmieder SJ, Harper CD, Schmieder GJ. *Granuloma Annulare*. StatPearls Publishing; 2022.
13. Marchand L, Villar-Fimbel S. Necrobiosis Lipoidica. *Am J Med*. 2020;133(3):e112. doi:10.1016/j.amjmed.2019.08.029
14. Hammer E, Lilienthal E, Hofer SE, Schulz S, Bollow E, Holl RW. Risk factors for necrobiosis lipoidica in type 1 diabetes mellitus. *Diabet Med*. 2017;34(1):86-92. doi:10.1111/dme.13138
15. Canna SW, Behrens EM. Not all hemophagocytes are created equally: appreciating the heterogeneity of the hemophagocytic syndromes. *Curr Opin Rheumatol*. 2012;24(1):113-118. doi:10.1097/BOR.0b013e32834dd37e
16. Jordan MB, Allen CE, Greenberg J, et al. Challenges in the diagnosis of hemophagocytic lymphohistiocytosis: recommendations from the north American consortium for histiocytosis (NACHO). *Pediatr Blood Cancer*. 2019;66(11):e27929. doi:10.1002/pbc.27929
17. Ahmed A, Merrill SA, Alsawah F, et al. Ruxolitinib in adult patients with secondary haemophagocytic lymphohistiocytosis: an open-label, single-Centre, pilot trial. *Lancet Haematol*. 2019;6(12):e630-e637. doi:10.1016/s2352-3026(19)30156-5

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Deng R, Meng X, Wang A, Li R. Cutaneous granuloma annulare in an adult patient with macrophage activation syndrome. *Clin Case Rep*. 2023;11:e7181. doi:10.1002/ccr3.7181