Febrile Ulceronecrotic Mucha-Habermann Disease: A Case Report and a Systematic Review

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Abstract
The characteristics and treatments of febrile ulceronecrotic Mucha-Habermann disease (FUM-HD) are not well-understood. We reported a FUMHD case, and searched Medline, Embase, Pubmed, Scopus, and Web of Science from inception to June 16, 2021, to perform a systematic review to synthesize its characteristics and treatments. Seventy-eight reports, including 84 people were eligible. Most of them were male (62/83, 74.7%), with high fever state (50/80, 62.5% had a high fever of 39°C or above), and with more positive skin bacterial cultures (31/41, 75.6%). Adults were associated with a higher risk of death (OR = 12.976, 95% CI: 1.049, 160.504, \(p = 0.046\)), but not positive blood bacterial cultures (\(p = 0.102\)). Systematic corticosteroids combination with other immunosuppressants (methotrexate or cyclosporine) were associated with significantly more effective cases (26/31 = 83.9%, \(\chi^2 = 4.065, p = 0.044\)). Furthermore, no significant differences between the low-dose and high-dose systematic corticosteroid groups were detected in treatment validation (\(p > 0.05\)). Overall, FUMHD was associated with male patients, high fever, and positive skin bacterial cultures. Early combination therapy with lower doses of corticosteroids and methotrexate or cyclosporine may be an optimal choice for the treatment of FUMHD.

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Introduction

Febrile ulceronecrotic Mucha-Habermann disease (FUMHD) is a rare and severe form of pityriasis lichenoides, which also includes two other types: pityriasis lichenoides et varioliformis acuta (PLEVA) and pityriasis lichenoides chronica [1]. FUMHD is a life-threatening disorder commonly referred to as a subtype of PLEVA, characterized by acute onset of generalized ulceronecrotic papules and plaques with fever and a rapidly progressive course without any tendency to spontaneously resolve [1, 2].

To the best of our knowledge, since FUMHD was firstly described by Degos et al. [3], only about 80 cases have been reported. Due to the low prevalence rate and consequently the absence of large well-designed studies necessary for etiology exploration and therapeutic effect evaluation, FUMHD represents a therapeutic challenge. The aim of this study was to add a case of FUMHD and to synthesize current evidence on its characteristics and treatment to facilitate clinical management.

Case Report

An 11-year-old Chinese boy (weight 40 kg) presented with a trunk erythematous papule approximately 2 weeks before presentation. On admission, he was afebrile, with densely distributed soy-sized erythematous maculopapular rashes on the trunk and extremities, without invasive necrotic scars. The oral and genital mucosa were not affected. Diagnosis of PLEVA was made based on clinical features and skin biopsy. Laboratory findings were normal except for decreased white blood count (WBC) (3.9 × 10⁹/L). Chest X-ray showed no abnormality. Screening for Epstein-Barr virus; varicella-zoster virus; morbillivirus; enterovirus 71; coxsackie B virus; herpes simplex virus; and HIV IgM antibodies, RPR, VDRL, and TPHA tests were negative. We started with mometasone furoate cream and tacrolimus ointment for 4 days. However, new rashes appeared, presenting with extensive pain, necrotic ulcerated papules and plaques, especially loose pustules in the groin, perineum, neck, and axilla, with a fever of 39°C. Follow-up blood test revealed elevated CRP (14 mg/L), aspartate aminotransferase (117 U/L), and alanine aminotransferase (54 U/L), respectively. A culture of skin was positive for methicillin-resistant Staphylococcus aureus and Pasteurella aerogenes, and flucloxacillin, methylprednisolone 1 mg/kg daily, oral methotrexate (MTX) 7.5 mg weekly, and topical mupirocin ointment were administered. The temperature returned to normal but the rash was still bright red, and the ulcer surface cannot dry up. Then, a dramatic response was obtained within 5 days when methylprednisolone was increased to 4 mg/kg. After about 2 months, most scabs fell off and left with widespread scarring (Fig. 1).

Discussion

We performed the searches in five electronic medical databases, including Medline, Embase, Pubmed, Scopus, and Web of Science from inception to June 16, 2021. The keywords used in the search were “febrile ulceronecrotic Mucha-Habermann,” “case report,” and their variations. We also searched the reference lists of all identified relevant studies for additional cases. No restrictions on languages were placed.

Three investigators (P.T., H.Y., and J.-s.C.) independently assessed documents. We included all the cases diagnosed with FUMHD, regardless of age, sex, treatment, and severity of disease. We excluded conference abstracts, reviews, duplicate articles, and some studies published in Italian, Japanese, and Korean. Three reviewers (P.T., H.Y., and H.W.) independently extracted
the age, sex, treatments, outcomes, and some treatable traits (TTs), including body temperature, mucosal involvement, duration of prehospital onset, inflammatory biomarkers (WBC, CRP, ESR), bacterial/virus infection, antinuclear antibodies, and liver function. Treatments were grouped into “valid” and “invalid,” while “valid treatment” stands for “the condition was relieved after treatment, including the return of body temperature to normal, and the gradual disappearance of skin lesions, etc.” and “invalid treatment” for “the condition did not relieve or even continue to aggravate after treatment, including uncontrolled fever, continuous progress of skin damage, etc.” We have cross-checked the information to ensure the accuracy
and completeness of the contents. Discrepancies in eligibility decisions were discussed at each stage of the process until the reviewers reached a joint consensus.

Statistical analyses were performed using SPSS software version 23.0 (SPSS, Inc.). Data are expressed as the means ± SD or median (quartile 1, quartile 3) or a percentage. Z-test and the χ²-test were used to detect the difference between two proportions. Logistic regression was used to evaluate associations. Differences with p < 0.05 were marked statistically significant.

Finally, we identified 343 references from electronic databases and nine additional works from reviews and references. After excluding duplicated articles and screened titles and abstracts, we filtered out 84 articles (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000525008). Finally, after further reviewing the full texts, and excluding those published in Italian (n = 2) [4, 5], Korean (n = 1) [6], and Japanese (n = 3) [7–9], we included 78 studies fulfilling the inclusion criteria and were able to provide data for further analyses (Fig. 2).

Including the patient we reported, this study included 84 patients, 43 children and 41 adults. The mean age of children was 9.90 ± 4.41 years, while the median age of reported adults case was 33 (23.5, 49) years. Of the reported cases in children and adults, 34/43 (79.1%) and 28/40 (70.0%) were male, respectively (Tables 1, 2).

During physical examination, 80/84 (95.24%) reported body temperature, of which 50/84 (62.5%) had high fever. Second, mucosal examination was performed in 50/84 (59.5%)
cases, of which 26/50 (52%) had mucosal involvement. In the inflammatory index survey, the levels of WBC, CRP, and ESR were increased in 21/54 (38.9%), 31/41 (75.6%), and 23/30 (76.7%), respectively. In the infection assessment, the positive bacterial cultures from skin and blood were 31/41 (75.6%) and 18/39 (46.2%), respectively, of which 19 (61.3%) and 7 (38.9%) were identified as *Staphylococcus aureus*. In addition, 12/64 (18.8%) were positive for viral infection. Among them, Epstein-Barr virus (4/12, 33.3%) was the virus with the most positive reports, followed by varicella-zoster virus (2/12, 16.7%). Abnormal liver function (26/47, 55.3%) was the most common organ involvement, and all antinuclear antibodies reports were negative. Ultimately, 17.9% (15/84) of patients died (online suppl. Table 2).

### Table 1. Clinical characteristics of the study participants with FUMHD, classified as child (age <18 years) or adult (age ≥ 18 years)

| Characteristic                     | n1 | Child (n = 43) | n2 | Adult (n = 41) | Z/χ² | p value |
|------------------------------------|----|---------------|----|---------------|------|---------|
| **General situation**              |    |               |    |               |      |         |
| Age, years, median (Q1, Q3), mean ± SD | 42 | 9.90±4.41     | 41 | 33 (23.5, 49) | -    | -       |
| Sex: male, n (%)                   | 43 | 34, 79.1      | 40 | 28, 70.0      | -0.944 | 0.345   |
| Onset, median (Q1, Q3)             | 39 | 21 (12, 28)   | 33 | 28 (14.5, 45) | -1.923 | 0.054   |
| **Physical examination**           |    |               |    |               |      |         |
| Fever, °C, median (Q1, Q3)         | 27 | 40 (39, 40)   | 26 | 39.5 (39, 40) | -0.442 | 0.658   |
| Mucosal involvement, n (%)         | 25 | 12, 48.0      | 26 | 14, 53.8      | -0.413 | 0.679   |
| **Laboratory examination**         |    |               |    |               |      |         |
| Abnormal WBC, n (%)                | 28 | 9, 32.1       | 26 | 16, 61.5      | -2.144 | 0.032   |
| Elevated CRP, n (%)                | 24 | 16, 66.7      | 17 | 15, 88.2      | -1.565 | 0.118   |
| Elevated ESR, n (%)                | 17 | 13, 76.5      | 13 | 10, 76.9      | 0.029  | 0.977   |
| Positive skin cultures, n (%)      | 19 | 13, 68.4      | 22 | 18, 81.8      | -0.984 | 0.325   |
| Positive blood cultures, n (%)     | 18 | 6, 33.3       | 21 | 12, 57.1      | 1.468  | 0.142   |
| Viral infection, n (%)             | 33 | 6, 18.2       | 31 | 6, 19.4       | 0.182  | 0.856   |
| Deranged liver function, n (%)     | 22 | 10, 45.5      | 25 | 16, 64.0      | 1.262  | 0.207   |
| Abnormal antinuclear antibodies    | 14 | 0             | 12 | 0             | -      | -       |
| **Outcomes**                       |    |               |    |               |      |         |
| Death, n, %                        | 43 | 2, 4.7        | 41 | 13, 31.7      | 8.711  | 0.003   |

### Table 2. Summary of treatments, classified as invalid and valid

|                   | Invalid (n = 57) | Valid (n = 70) | χ²  | p value |
|-------------------|-----------------|---------------|-----|---------|
| Corticosteroids, n (%) | 44 (49.4)       | 45 (50.6)     | 2.496 | 0.114   |
| MTX, n (%)         | 8 (18.2)        | 36 (81.8)     | 19.402 | 0.000   |
| Cyclosporine, n (%) | 3 (33.3)        | 6 (66.7)      | 0.141  | 0.708   |
| Antibiotics, n (%)  | 38 (55.9)       | 30 (44.1)     | 7.160  | 0.007   |
| Antiviral, n (%)    | 14 (77.8)       | 4 (22.2)      | 7.690  | 0.006   |
| IVIG, n (%)         | 9 (56.3)        | 7 (43.8)      | 0.956  | 0.328   |
| Dapsone, n (%)      | 2 (40)          | 3 (60)        | 0     | 1.000   |
| UVB, n (%)          | 0               | 3 (100)       | -     | 0.252   |
| Pentoxifylline, n (%) | 0              | 2 (100)       | -     | 0.501   |
Furthermore, as shown in Table 1, comparing the TTs of the children and adult groups, we found no significant differences other than WBC counts and the outcomes. When adults (61.5%) had significantly higher (\(p = 0.032\)) WBC count abnormalities (increase and decrease) than children (32.1%), adults (31.7%) also had significantly higher mortality (\(p = 0.003\)) than children (4.7%).

First, univariate analysis found that the significant differences between the cured and dead groups were age (\(p = 0.000\)), sex (\(p = 0.046\)), and blood culture results (\(p = 0.025\)). In addition, the logistic regression model found that compared with children, adults had a statistically significant increased risk of death (OR = 12.976, 95% CI: 1.049, 160.504, \(p = 0.046\)). Furthermore, after adjusting for gender and age, the logistic regression model found no significantly increased risk of death in patients with positive blood bacterial cultures compared with those with negative blood cultures (\(p = 0.102\)).

We summarized all the managements in the cases. Among the treatments for immunosuppression, systemic corticosteroids (68/84, 81.0%) were the most commonly used, followed by MTX (42/84, 50%) and cyclosporine (8/84, 9.5%). In addition, 2 (2.4%) cases were successfully treated with TNF-\(\alpha\) inhibitor, and one (1.2%) was successfully treated with lymphoplasmapheresis, skin grafting, and antipyretic therapy, respectively (online suppl. Table 3).

Furthermore, in order to explore and evaluate effective treatments, we kept track of all treatments, both effective and ineffective, monotherapy and combination therapy. Therefore, percentages did not total 100% because many patients received more than one therapeutic regimen, including initial treatments that did not work, and treatments that later worked or remained ineffective. Finally, we recorded 127 therapeutic regimens, of which 57 were ineffective and 70 were effective. A comparative study of ineffective and effective treatments groups found that MTX was associated with significantly more effective cases (81.8%, \(\chi^2 = 19.402, p = 0.000\)), but antibiotics (55.9%, \(\chi^2 = 7.160, p = 0.007\)) and antiviral drugs (77.8%, \(\chi^2 = 7.69, p = 0.006\)) were associated with significantly more ineffective cases. No significant differences in therapeutic efficacy were found with and without systemic corticosteroids, cyclosporine, IVIG, dapsone, UVB, and pentoxifylline, respectively (\(p > 0.05\)) (Table 2).

In order to explore the necessity and appropriate administration of systemic glucocorticoids, we compared the effective and ineffective cases in the treatment group with systemic corticosteroids and those without immunosuppressants and found no significant differences (\(\chi^2 = 0.207, p = 0.649\)). However, in detail, the group of systemic corticosteroids in combination with other immunosuppressants (MTX or cyclosporine) was associated with significantly higher effective cases (26/31 = 83.9%, \(\chi^2 = 4.065, p = 0.044\)), while systemic corticosteroid monotherapy was not significantly different from non-immunosuppressive therapy (\(\chi^2 = 3.562, p = 0.059\)) (online suppl. Table 4).

Furthermore, subgroup analyses according to dosage of systemic corticosteroids and age of patients were performed to explore the appropriate dosage in the combination therapy group, and we found that there were no significant differences between low-dose (children, \(\leq 2\) mg/kg/day; adults, \(\leq 60\) mg/day or 1 mg/kg/day) and high-dose groups (children, \(>2\) mg/kg/day; adults, \(>60\) mg/day or 1 mg/kg/day) in the treatment validation in all the subgroup of children (\(p = 0.350\)), adults (\(p = 1.000\)), and total patients (\(p = 1.000\)) (online suppl. Table 4).

We added a new case of FUMHD in this study, which, to our knowledge, is the first systematic review of the clinical characteristics and treatment of FUMHD. Our results indicated that most of the patients were males, in high fever state, with increased CRP and ESR levels, and more positive bacterial cultures, especially on the skin. In terms of treatment, we found that combined immunosuppressive therapy (systematic corticosteroids in combination...
with MTX or cyclosporine) was superior to non-immunosuppressive therapy and that high-dose corticosteroids were similar in efficacy to low-dose corticosteroids.

In the non-TTs, we found that FUMHD occurred mainly in school-age (mean age: 9.9 years) and young (median age: 33 years) male patients. Current evidence suggests that the median time from the onset of symptoms (including fever or rash) to diagnosis of FUMHD is about 25 days, 21 days in children and 28 days in adults. It suggests that we need to be vigilant that school-age boys and young men with PLEVA may progress to FUMHD, and the incubation period of about 25 days, which is conducive to early diagnosis and treatment.

In the TTs of physical examination, current evidence shows that patients with FUMHD usually had a high fever of 39°C or higher. Furthermore, mucosal involvement is not a specific feature of FUMHD, as only about half of the patients had mucosal involvement (children: 48%, adults: 53.8%).

In the assessment of inflammatory index, we found that most patients (about 75%) had elevated levels of CRP and ESR, while WBC was normal (53.7%). This may be due to the low sensitivity and slow response of WBC [10], whereas CRP and ESR respond rapidly in inflammatory states [11]. Actually, a comparison of pediatric and adult cases found that both the duration of prehospital disease and incidence of WBC abnormalities were lower in the pediatric group, but the levels of CRP and ESR were similar to those in adults’ group, which is consistent with the slow response characteristics of leukocyte detection. Moreover, current evidence suggests that pediatric cases with lower mortality rate (4.7%) had a significantly favorable outcome. Above all, it seems that the abnormal WBC count is correlated with mortality. However, based on the available data, we found no correlation between the two. Due to the lack of a large amount of data, this conclusion needs to be verified with more data in the future.

The etiology and pathogenesis of FUMHD remain uncertain. It used to be thought that FUMHD was associated with virus infection [2]. However, only 18.8% of the reported cases had evidence of viral infection, but positive bacterial cultures were more common, especially on the skin (75.6%). In addition, treatments of systemic corticosteroids in combination with other immunosuppressants (MTX or cyclosporine) were associated with significantly more valid cases, which supported the proposition that the pathogenesis of FUMHD may be related to the activation of immune response induced by skin surface bacteria [12].

Furthermore, since sepsis is thought to be associated with death [13, 14], we analyzed the association between infection and outcome but found that neither positive blood nor skin cultures for bacteria were associated with the end of death. Our subsequent treatment study revealed that anti-infective therapy was ineffective in most FUMHD cases, which indirectly confirmed this conclusion. Moreover, current evidence suggests that adults are associated with a higher risk of death, a finding that contributes to scientifically valid doctor-patient communication in clinical work. In addition, we found no association between outcome measures and other factors, including sex, onset, CRP, ESR, WBC, and liver function. More detailed data, such as the correlation study between the timing of MTX use and prognosis, are needed.

In addition, of all treatment regimens, only MTX showed significant improvement. Our study found that systemic corticosteroids alone, with or without other non-immunosuppressive therapies (antibiotics, antiviral, and IVIG) showed similar therapeutic validation to non-immunosuppressive therapies. However, their combination with other immunosuppressants (MTX or cyclosporine) was associated with significantly higher efficacy. This suggests that systemic corticosteroids in combination with MTX or cyclosporine are optimal therapy for FUMHD. However, since infection is often consistent with FUMHD, the optimal dose of systemic corticosteroids needs to be explored. Subgroup analyses based on systemic corticosteroids do found no significant difference in validation between higher and lower doses. Therefore, considering the risk of worsening infection, a lower dose of corticosteroids (≤2 mg/kg/day in children; ≤60 mg/day or 1 mg/kg/day in adults) is clinically preferable.
Our review had several limitations. In addition to limited available data, the included cases have an inherent weakness that some cases reported in the literature did not meet the diagnostic criteria for FUMHD [12] and therefore cannot be considered real cases.

**Conclusion**

FUMHD is typically associated with high fever, elevated CRP and ESR, positive bacterial cultures of the skin, and liver dysfunction. School-aged boys and young men are more susceptible. Early combination therapy of lower doses of corticosteroids and MTX or cyclosporine may be an optimal choice for the treatment of FUMHD.

**Statement of Ethics**

Written informed consent was obtained from the parent/legal guardian of the patient for publication of the details of their medical case and any accompanying images. The study has been done according to the Declaration of Helsinki. Ethical approval was not required for this study in accordance with national guidelines.

**Conflict of Interest Statement**

The authors have no conflicts of interest.

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**Author Contributions**

Ping Tang was in contact with the patient, obtained written consent, diagnosed the patient, and drafting the manuscript. Jing-si Chen and Hua Wang contributed to data curation and software. Huan Yang contributed as corresponding author to conceptualization, methodology, project administration, and submitting the final version.

**Data Availability Statement**

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

**References**

1. Bowers S, Warshaw EM. Pityriasis lichenoides and its subtypes. *J Am Acad Dermatol*. 2006 Oct;55(4):557–6; quiz 573–6.
2. Khachemoune A, Blyumin ML. Pityriasis lichenoides: pathophysiology, classification, and treatment. *Am J Clin Dermatol*. 2007;8(1):29–36.
Degos R, Duperrat B, Daniel F. Le parapsoriasis ulcéro-nécrotique hyperthermique. Forme suraiguë du parapsoriasis en gouttes [Hyperthermic ulcer-necrotic parapsoriasis. Subacute form of parapsoriasis guttata]. Ann Dermatol Syphiligr. 1966 Oct–Dec;93(5):481–96.

Reseghetti A, Parma A, Rozzoni M, Cainelli G. Febrile ulceronecrotic pityriasis lichenoides et varioliformis acuta. Giorn Ital Dermat V. 1996 Jan;131(1):55–8.

Carcattera A, Santini M, Fideli D. Ulcero-necrotic pityriasis lichenoides et varioliformis acuta (PLEVA). Annali Italiani di Dermatologia Clinica e Sperimentale. 1997 Jan;51(2):50–5.

Kwon, Lim, Suh, Kim. A case of febrile ulceronecrotic mucha-habermann’s disease in an infant. Korean J Dermatol. 2005 Feb;43(2):267–70.

Kasamatsu M, Yokota M, Morita A, Tsuji T, Ichiki T, Mizuno M, et al. A case of febrile ulceronecrotic Mucha-Habermann’s disease. Nishinihon J Dermatol. 1993;55(4):665–9.

Tsuji T, Kasamatsu M, Yokota M, Morita A, Schwartz RA. Mucha-Habermann disease and its febrile ulceronecrotic variant. Cuts. 1996 Aug;58(2):123–31.

Ashida M, Hamasaki Y, Shimizu K, Toriyama F. Febrile ulceronecrotic Mucha-Habermann’s disease with multiple drug-hypersensitivity in anti-HTLV-1 antibody positive patient. Nishinihon J Dermatol. 2004;66(2):169–74.

Korppi M, Kröger L, Laitinen M. White blood cell and differential counts in acute respiratory viral and bacterial infections in children. Scand J Infect Dis. 1993;25(4):435–40.

Breda L, Nozzi M, De Sanctis S, Chiarelli F. Laboratory tests in the diagnosis and follow-up of pediatric rheumatic diseases: an update. Semin Arthritis Rheum. 2010 Aug;40(1):53–72.

Nofal A, Assaf M, Alakad R, Amer H, Nofal E, Yosef A. Febrile ulceronecrotic Mucha-Habermann disease: proposed diagnostic criteria and therapeutic evaluation. Int J Dermatol. 2016 Jul;55(7):729–38.

Cazzio A, Haňer J, Kempi W, Höffner A, Palmedo G, Michaels S, et al. Febrile ulceronecrotic Mucha-Habermann disease with clonality: a cutaneous T-cell lymphoma entity? J Am Acad Dermatol. 2004 Dec;51(6):1014–7.

Aytekin S, Balci G, Duzgun OY. Febrile ulceronecrotic Mucha-Habermann disease: a case report and a review of the literature. Dermatol Online J. 2005 Dec 1;11(3):31.