

Febrile Ulceronecrotic Mucha-Habermann Disease: A Rare Form of Pityriasis Lichenoides et Varioliformis Acuta

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PRACTICE POINTS

- Febrile ulceronecrotic Mucha-Habermann disease (FUMHD) is a rare variant of pityriasis lichenoides et varioliformis acuta, characterized by ulceronecrotic lesions, fever, and systemic symptoms.
- A variety of treatments including immunosuppressive drugs (eg, systemic steroids, methotrexate), antibiotics, antivirals, phototherapy, intravenous immunoglobulin, and dapsone have been used in patients with FUMHD.

To the Editor:

Pityriasis lichenoides is a papulosquamous dermatologic disorder that is characterized by recurrent papules.¹ There is a spectrum of disease in pityriasis lichenoides that includes pityriasis lichenoides et varioliformis acuta (PLEVA) at one end and pityriasis lichenoides chronica at the other. Pityriasis lichenoides et varioliformis acuta is more common in younger individuals and is characterized by erythematous papules that often crust; these lesions resolve over weeks. The lesions of pityriasis lichenoides chronica are characteristically scaly, pink to red-brown papules that tend to resolve over months.¹

Histologically, PLEVA exhibits parakeratosis, interface dermatitis, and a wedge-shaped infiltrate.¹ Necrotic keratinocytes and extravasated erythrocytes also are common features. Additionally, monoclonal T cells may be present in the infiltrate.¹

Febrile ulceronecrotic Mucha-Habermann disease (FUMHD) is a rare and severe variant of PLEVA. Febrile ulceronecrotic Mucha-Habermann disease is characterized by ulceronecrotic lesions, fever, and systemic symptoms.² Herein, we present a case of FUMHD.

A 57-year-old man presented with an eruption of painful lesions involving the face, trunk, arms, legs, and genitalia of 1 month's duration. The patient denied oral and ocular involvement. He had soreness and swelling of the arms and legs. A prior 12-day course of prednisone prescribed by a community dermatologist failed to improve the rash. A biopsy performed by a community dermatologist was nondiagnostic. The patient denied fever but did report chills. He had no preceding illness and was not taking new medications. On physical examination, the patient was afebrile and normotensive with innumerable deep-seated pustules and crusted ulcerations on the face, palms, soles, trunk, extremities, and penis (Figures 1 and 2). There was a background morbilliform eruption on the trunk. The ocular and oral

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mucosae were spared. The upper and lower extremities had pitting edema.

The patient's alanine aminotransaminase and aspartate aminotransaminase levels were elevated at 55 and 51 U/L, respectively. His white blood cell count was within reference range; however, there was an elevated absolute neutrophil count ($8.7 \times 10^3/\mu\text{L}$). No eosinophilia was noted. Laboratory evaluation showed a positive anti-mitochondrial antibody, and magnetic resonance imaging showed evidence of steatohepatitis. Punch biopsies from both the morbilliform eruption and a deep-seated pustule showed epidermal necrosis, parakeratosis, necrotic keratinocytes, and a lichenoid infiltrate of lymphocytes at the dermoepidermal interface. In the dermis, there was a wedge-shaped superficial and deep, perivascular infiltrate with extravasated erythrocytes (Figures 3 and 4). Tissue

Gram stain was negative for bacteria. Varicella-zoster virus and herpes simplex virus immunostains were negative. Direct immunofluorescence showed colloid bodies, as can be seen in lichenoid dermatitis.

At the next clinic visit, the patient reported a fever of 39.4°C . After reviewing the patient's histopathology and clinical picture, along with the presence of fever, a final diagnosis of FUMHD was made. The patient was started on an oral regimen of prednisone 80 mg once daily, minocycline 100 mg twice daily, and methotrexate 15 mg weekly. Unna boots (specialized compression wraps) with triamcinolone acetone ointment 0.1% were placed weekly until the leg edema and ulcerations healed. He was maintained on methotrexate 15 mg weekly and 5 to 10 mg of prednisone once daily. The patient demonstrated residual scarring, with only rare new papulonodules that did not ulcerate when attempts were made to taper his medications. He was followed for nearly 3 years, with a recurrence of symptoms 2 years and 3 months after initial presentation to the academic dermatology clinic.



FIGURE 1. Febrile ulceronecrotic Mucha-Habermann disease. Ulcerative and crusted violaceous papules on the extremities and trunk.



FIGURE 2. Febrile ulceronecrotic Mucha-Habermann disease. Ulcerative and crusted violaceous papules on the right palm.

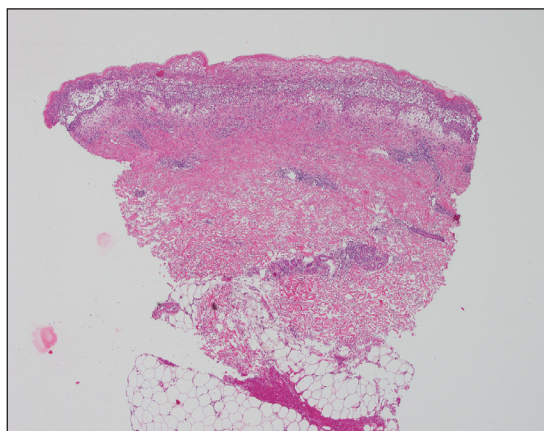


FIGURE 3. Histopathology showed a lichenoid infiltrate and a wedge-shaped lymphocytic perivascular infiltrate (H&E, original magnification $\times 40$).

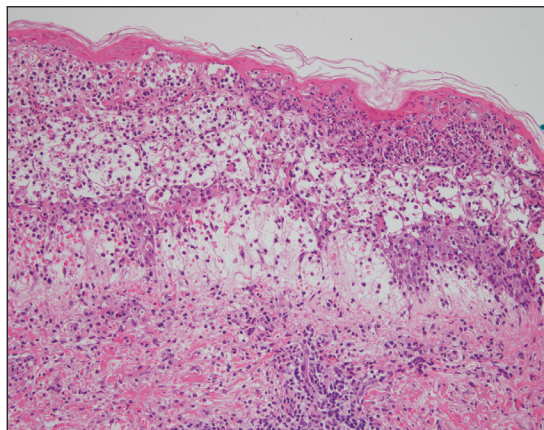


FIGURE 4. Histopathology showed extravasated erythrocytes and lymphocytes (H&E, original magnification $\times 200$).

Febrile ulceronecrotic Mucha-Habermann disease is a rare and severe variant of PLEVA that can present with the rapid appearance of necrotic skin lesions, fever, and systemic manifestations, including pulmonary, gastrointestinal, central nervous system, cardiac, hematologic, and rheumatologic symptoms.²⁻⁴ The evolution from PLEVA to FUMHD ranges from days to weeks, and patients rarely can have an initial presentation of FUMHD.² The duration of illness has been reported to be 1 to 24 months⁵; however, the length of illness still remains unclear, as many studies of FUMHD are case reports with limited follow-up. Our patient had a disease duration of at least 27 months. The lesions of FUMHD usually are generalized with flexural prominence, and mucosal involvement occurs in approximately one-quarter of cases. Hypertrophic scarring may be seen after the ulcerated lesions heal.² The incidence of FUMHD is higher in men than in women, and it is more common in younger individuals.^{2,6} There have been reported fatalities associated with FUMHD, mostly in adults.^{2,4}

The clinical differential diagnosis for PLEVA includes disseminated herpes zoster, varicella-zoster virus or coxsackievirus infections, lymphomatoid papulosis, angiodesstructive lymphoma such as extranodal natural killer/T-cell lymphoma, drug eruption, arthropod bite, erythema multiforme, ecthyma, ecthyma gangrenosum, necrotic folliculitis, and cutaneous small vessel vasculitis. To differentiate between these diagnoses and PLEVA or FUMHD, it is important to take a strong clinical history. For example, for varicella-zoster virus and coxsackievirus infections, exposure history to the viruses and vaccination history for varicella-zoster virus can help elucidate the diagnosis.

Skin biopsy can help differentiate between these entities and PLEVA or FUMHD. The histopathology of a nonulcerated lesion of FUMHD shows parakeratosis, spongiosis, and lymphocyte exocytosis, as well as lymphocytic vasculitis—findings commonly seen in PLEVA. With the ulceronecrotic lesions of FUMHD, epidermal necrosis and ulceration can be seen microscopically.² Although skin biopsy is not absolutely necessary for making the diagnosis of PLEVA, it can be helpful.³ However, given the dramatic and extreme clinical impression with an extensive differential diagnosis that includes disorders ranging from infectious to neoplastic, biopsy of FUMHD with clinicopathologic correlation often is required.

It is important to avoid biopsying ulcerated lesions of FUMHD, as the histopathologic findings are more likely to be nonspecific. Additionally, nonspecific features often are seen with immunohistochemistry; abnormal laboratory testing may be seen in FUMHD, but there is no specific test to diagnose FUMHD.² Finally, a predominantly CD8⁺ cell infiltrate was seen in 4 of 6 cases of FUMHD, with 2 cases showing a mixed infiltrate of CD8⁺ and CD4⁺ cells.^{5,7-10}

Although no unified diagnostic criterion exists for FUMHD, Nofal et al² proposed criteria comprised of

constant features, which are found in every case of FUMHD and can confirm the diagnosis alone, and variable features to help ensure that cases of FUMHD are not missed. The constant features include fever, acute onset of generalized ulceronecrotic papules and plaques, a course that is rapid and progressive (without a tendency for spontaneous resolution), and histopathology that is consistent with PLEVA. The variable features include history of PLEVA, involvement of mucous membranes, and systemic involvement.²

No single unifying treatment modality for all cases of FUMHD has been described. Immunosuppressive drugs (eg, systemic steroids, methotrexate), antibiotics, antivirals, phototherapy, intravenous immunoglobulin, and dapsone have been tried in patients with FUMHD.² Combination therapy with an oral medication such as erythromycin or methotrexate and psoralen plus UVA may be effective for FUMHD.³ Additionally, some authors believe that patients with FUMHD should be treated similar to burn victims with intensive supportive care.²

The etiology of PLEVA is unknown, but it is presumed to be associated with an effector cytotoxic T-cell response to either an infectious agent or a drug.¹¹ Three studies have shown that most PLEVA cases (100% [3/3]; 65% [13/20]; and 57% [8/14]) demonstrate T-cell clonality,¹²⁻¹⁴ and some have suggested that PLEVA may be a T-cell lymphoproliferative disorder.^{12,13} Additionally, in a case report of 2 children with PLEVA who progressed to cutaneous T-cell lymphoma, the authors suggested that PLEVA may be related to nonaggressive cutaneous T-cell lymphoma.¹⁵ Of note, T-cell clonality, often found through the analysis of T-cell receptor gene rearrangement, is not an absolute criterion for determining malignancy, as some benign conditions may have clonality.¹⁶ However, in another study, clonality was found in only 1 of 10 cases of PLEVA, suggesting that PLEVA stems from an inflammatory reaction to infectious or other triggering agents.¹⁷

Four cases of FUMHD with monoclonality have been reported,^{4,7,8} and some researchers propose that FUMHD may be a subset of cutaneous T-cell lymphoma.⁷ However, 2 other cases of FUMHD did not show monoclonality of T cells,^{5,18} suggesting that FUMHD may represent an inflammatory disorder, rather than a lymphoproliferative process of T cells.¹⁸ Given the controversy surrounding the clonality of FUMHD, T-cell gene rearrangement studies were not performed in our case.

REFERENCES

1. Bologna JL, Schaffer JV, Duncan KO, et al. Other papulosquamous disorders. In: Bologna JL, Schaffer JV, Duncan KO, et al, eds. *Dermatology Essentials*. Elsevier Saunders; 2014:68-69.
2. Nofal A, Assaf M, Alakad R, et al. Febrile ulceronecrotic Mucha-Habermann disease: proposed diagnostic criteria and therapeutic evaluation. *Int J Dermatol*. 2016;55:729-738.
3. Milligan A, Johnston GA. Pityriasis lichenoides et varioliformis acuta. In: Lebowitz MG, Heymann WR, Berth-Jones J, et al, eds.

- Treatment of Skin Disease, Comprehensive Therapeutic Strategies*. 4th ed. Saunders; 2013:580-582.
4. Miyamoto T, Takayama N, Kitada S, et al. Febrile ulceronecrotic Mucha-Habermann disease: a case report and a review of the literature. *J Clin Pathol*. 2003;56:795-797.
 5. Meziane L, Caudron A, Dhaille F, et al. Febrile ulceronecrotic Mucha-Habermann disease: treatment with infliximab and intravenous immunoglobulins and review of the literature. *Dermatology*. 2012;225:344-348.
 6. Robinson AB, Stein LD. Miscellaneous conditions associated with arthritis. In: Kliegman RM, Stanton BF, St. Geme JW III, et al, eds. *Nelson Textbook of Pediatrics*. 19th ed. W.B. Saunders Company; 2011:880.
 7. Cozzio A, Hafner J, Kempf W, et al. Febrile ulceronecrotic Mucha-Habermann disease with clonality: a cutaneous T-cell lymphoma entity? *J Am Acad Dermatol*. 2004;51:1014-1017.
 8. Tsianakas A, Hoeger PH. Transition of pityriasis lichenoides et varioliformis acuta to febrile ulceronecrotic Mucha-Habermann disease is associated with elevated serum tumour necrosis factor-alpha. *Br J Dermatol*. 2005;152:794-799.
 9. Yanaba K, Ito M, Sasaki H, et al. A case of febrile ulceronecrotic Mucha-Habermann disease requiring debridement of necrotic skin and epidermal autograft. *Br J Dermatol*. 2002;147:1249-1253.
 10. Lode HN, Döring P, Lauenstein P, et al. Febrile ulceronecrotic Mucha-Habermann disease following suspected hemorrhagic chickenpox infection in a 20-month-old boy. *Infection*. 2015;43:583-588.
 11. Tomasini D, Tomasini CF, Cerri A, et al. Pityriasis lichenoides: a cytotoxic T-cell-mediated skin disorder: evidence of human parvovirus B19 DNA in nine cases. *J Cutan Pathol*. 2004;31:531-538.
 12. Weiss LM, Wood GS, Ellisen LW, et al. Clonal T-cell populations in pityriasis lichenoides et varioliformis acuta (Mucha-Habermann disease). *Am J Pathol*. 1987;126:417-421.
 13. Dereure O, Levi E, Kadin ME. T-cell clonality in pityriasis lichenoides et varioliformis acuta: a heteroduplex analysis of 20 cases. *Arch Dermatol*. 2000;136:1483-1486.
 14. Weinberg JM, Kristal L, Chooback L, et al. The clonal nature of pityriasis lichenoides. *Arch Dermatol*. 2002;138:1063-1067.
 15. Fortson JS, Schroeter AL, Esterly NB. Cutaneous T-cell lymphoma (parapsoriasis en plaque): an association with pityriasis lichenoides et varioliformis acuta in young children. *Arch Dermatol*. 1990;126:1449-1453.
 16. Bologna JL, Schaffer JV, Duncan KO, et al. Cutaneous T-cell lymphoma. In: Bologna JL, Schaffer JV, Duncan KO, et al, eds. *Dermatology Essentials*. Elsevier Saunders; 2014:958.
 17. Kim JE, Yun WJ, Mun SK, et al. Pityriasis lichenoides et varioliformis acuta and pityriasis lichenoides chronica: comparison of lesional T-cell subsets and investigation of viral associations. *J Cutan Pathol*. 2011;38:649-656.
 18. López-Estebarráz JL, Vanaclócha F, Gil R, et al. Febrile ulceronecrotic Mucha-Habermann disease. *J Am Acad Dermatol*. 1993;29(5, pt 2):903-906.