Mortality risk factors in febrile ulceronecrotic Mucha-Habermann disease: A systematic review of therapeutic outcomes and complications

Vasiliki Tasouli-Drakou,[1] May Nguyen,[1] Hannah Guinn,[2] Omron Hassan,[1] Sneha Butala,[3] Sheshanna Phan[1,3]

[1]Department of Clinical Education, College of Osteopathic Medicine, Touro University Nevada, Henderson, NV; [2]Department of Physician Assistant Studies, College of Health and Human Services, Touro University Nevada, Henderson, NV; [3]Department of Dermatology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

Abstract

Febrile Ulceronecrotic Mucha-Habermann Disease (FUMHD) is a variant of Pityriasis Lichenoides Et Varioliformis Acuta (PLEVA). Although rare, the condition may progress to involve serious complications and even lead to fatal outcomes if diagnosis and appropriate treatment is delayed. A PubMed search following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) guidelines was performed to find cases of FUMHD from the earliest records to October 2021. Treatments, complications, and patient outcomes were extracted from the literature and summarized, while a review of quality was also performed. A total of 63 publications with 68 patients were found. Successful treatment modalities for FUMHD included antibiotics, antivirals, systemic steroids, Methotrexate (MTX), cyclophosphamide, Cyclosporine (CYA), Intravenous Immunoglobulins (IVIG), pentoxifylline, and ultraviolet B phototherapy. Out of 68 patients, 55 patients had their condition fully resolved and 13 cases were fatal. Increased age, systemic involvement, and monoclonal T-cell receptor rearrangement were associated with worst prognosis, but mucosal involvement did not affect mortality risk. Overall, the publications had low risk of bias, but most lacked adequate follow-up periods. FUMHD is a diagnostic and therapeutic challenge due to the lack of clearly defined diagnostic criteria and optimum treatment. Further studies with larger patient populations and longer follow-up periods may lead to refinement of diagnostic criteria, establish an optimum treatment regimen, and better estimate the likelihood of recurrence.

Introduction

Febrile Ulceronecrotic Mucha-Habermann Disease (FUMHD) is a severe subtype of Pityriasis Lichenoides Et Varioliformis Acuta (PLEVA) and was first reported in 1966.[1] Similarly to PLEVA, skin lesions in FUMHD are initially scaly papules and blisters that commonly affect flexor surfaces and may involve mucosal membranes,[2,3] but they quickly progress into necrotic ulcers that easily become secondarily infected.[4,5] FUMHD is also associated with high fevers and systemic complications related to splenomegaly, cardiomyopathy, pulmonary involvement, and sepsis.[6,7]

FUMHD presents diagnostic challenges as initial misdiagnosis may often occur, particularly during the early periods of the condition when it can often resemble PLEVA, chickenpox, or Steven-Johnson Syndrome (SJS).[7-10] Recent criteria have been proposed to help distinguish it, but laboratory abnormalities and histopathology are nonspecific and there are no specific tests that yield diagnosis.[7]

Currently, there are no universal guidelines for treatment of FUMHD. Common treatments reported in the literature include antibiotics, antivirals, systemic steroids, MTX, CYA, other immunosuppressants/immunomodulators, IVIG, and phototherapy.[7] Early treatment may increase the potential for recovery and resolution of fever, and the ulceronecrotic lesions may heal but can lead to long-term cosmetic defects, such as hypopigmentation and atrophic scars.[6] Blohm *et al.* proposed a calculation for mortality risk that may help guide healthcare providers on indications for more aggressive treatment of patients who are refractory to initial modalities.[11]

This is the first systematic review to discuss the outcomes of FUMHD treatment. Due to the lack of consensus on initial diagnosis and treatment of FUMHD, the aim of this systematic review is to provide a comprehensive review of the potential treatments and their success in treating patients with FUMHD. A meta-analysis was not conducted due to the small sample size and lack of homogeneity across studies.

Materials and Methods

This systematic review was conducted in accordance with PRISMA guidelines. Articles were retrieved from the PubMed database using the search formula: "febrile ulceronecrotic mucha-habermann" OR "febrile ulcerative mucha-habermann" OR "FUMHD." Given that FUMHD is a rare disease, no restrictions were applied to the year of publication and all articles from the earliest record to October 2021 were included.

Inclusion and exclusion criteria

During the initial screening, two inde-

Correspondence: Sheshanna Phan, Department of Dermatology, Feinberg School of Medicine, Northwestern University, 676 N St Clair Street, Suite 1600, Chicago, IL 60611, USA.
Tel.: 1.657.222.5078.
E-mail: sheshanna.phan@northwestern.edu

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pendent reviewers (V.T. and H.G.) assessed each article's title and abstract to exclude articles that were reviews or published abstracts, not in English, not published in a peer-reviewed journal, did not use human subjects, and did not treat at least 50% of subjects for FUMHD. Subsequently, two independent reviewers (V.T. and M.N.) screened the remaining publications by evaluating them in their entirety based on the following inclusion criteria: article is in English, FUMHD is the main disease reported, and publication includes treatment for FUMHD. In the case of disagreement, a third reviewer (S.P.) made the decision to include or exclude a publication after reviewing the study.

Quality assessment

Two independent reviewers (V.T. and M.N.) assessed the quality of each publication using the Joanna Briggs Institute Critical Appraisal Checklist for Case Reports. In the event that there was a disagreement between reviewers regarding the score of an article, a third reviewer (S.P.) decided the final score for that article.

There were nine criteria used to assess the quality of the publication, including clearly described demographics, patient history with timeline, patient's current clinical condition, diagnostic tests, treatment, patient outcome, identification of adverse effects, appropriate follow-up period, and takeaway lessons. A follow-up period of 9 months or more was considered adequate. As there are no current systematic reviews or cohort studies on FUMHD to determine the average time to recurrence, the time period to relapse in PLEVA was used.[4] Each publication was reviewed and assigned a score of 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate) for each criterion, and individual scores were then summed together to generate an overall score for each study. The maximum score that a publication could obtain was a score of 18.

Measure of patient outcome

For the purpose of this study, treatment outcomes were divided into two categories: resolved or fatal. Cases were considered resolved if there was resolution of skin lesions and systemic complication, even if continued treatment was required to prevent recurrence. Adverse effects were identified and recorded when available.

Selected studies and their characteristics

The process of study selection is summarized in Figure 1. The initial search of PubMed resulted in 80 articles, of which 23 articles were excluded. An extended search found six additional publications that met the inclusion criteria, yielding a total of 63 publications.

Table 1 summarizes the demographics of the 68 patients from the 63 publications. Female patients constituted 29.4% (20/68) and male patients 69.1% (47/68) of subjects, and the sex of one patient was unspecified.[12] Patient ages ranged from 9 months to 82 years.

The mean ages of patients in the resolved and fatal cohorts were 16 and 50 years old, respectively. Out of the 13 fatal cases, 69.2% (9/13) were over 40 years old.[5,12-22] Among the 55 patients whose condition was considered resolved, 78.2% (43/55) were male, and 21.8% (12/55) were female.[2,3,8-11,23-67] Among the 13 patients with fatal outcomes, 38.5% (5/13) were male, 53.8% (7/13) were female, and 7.7% (1/13) had unspecified gender.[12]

Summary of disease course

A potential trigger was identified in 17.6% (12/68) of FUMHD cases and were most commonly infectious in etiology including mycoplasma,[11] Varicella Zoster Virus (VZV),[33] parvovirus B19,[45] Epstein-Barr Virus (EBV),[30,51,66] Herpes Simplex Virus 2 (HSV-2),[56] Cytomegalovirus (CMV),[57] and adenovirus type II.[24] Other potential triggers reported include a spider bite,[38] measles vaccine,[67] and nonfebrile enteritis.[58]

Authors only mentioned whether or not there was mucosal involvement in 40 patients. Among these 40 patients, 52.5% (21/40) had mucosal involvement and 47.5% (19/40) did not. The majority of patients with mucosal involvement are in the resolved cohort, but the same ratio (31%) of patients in both the resolved (17/55) and fatal cohort (4/13) had mucosal involvement.

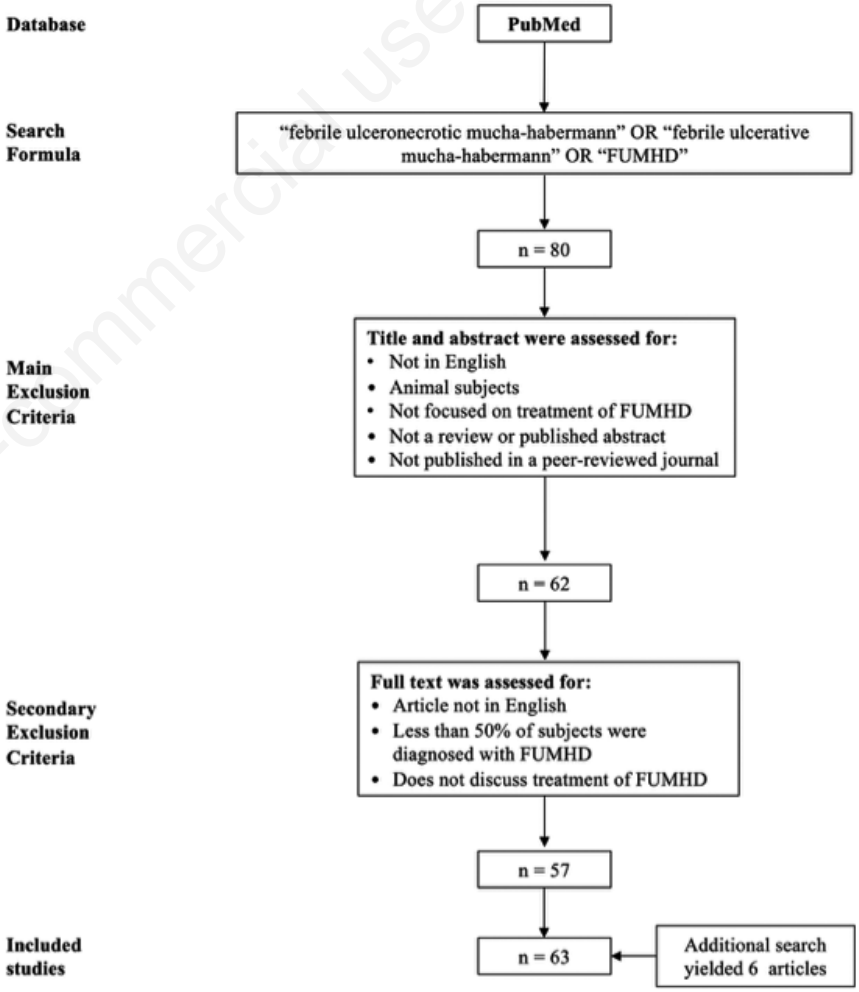

Figure 1. Flowchart depicting selection process of publications for this systematic review, number of publications (n).

Table 1. Summary of patient demographics and disease course. All patients had an associated fever even if no other systemic symptoms were reported.

Publication	Subject Age	Sex	Possible Etiology involvement	Mucosal	Systemic complications & abnormal labs
Blohm *et al.* (2021)	13 y	M	Mycoplasma infection	Yes	Conjunctivitis; oliguria; thrombocytopenia; elevated CRP, ferritin, and procalcitonin
Ngo *et al.* (2021)	43 y	F	NR	No	Lymphocytosis, hyponatremia, hypochloremia, hypoalbuminemia, elevated AST and ALT
Wu *et al.* (2021)	7 y	M	NR	NR	Elevated CRP, IL-6, IL-8, IL-10, interferon-γ, and TNF-α levels
Schaan *et al.* (2020)	NR	M	NR	No	Elevated CRP
Wang *et al.* (2020)	11 y	M	NR	NR	NR
Weins *et al.* (2020)	9 m	M	NR	Yes	Microcytic anemia, cervical lymphadenopathy, conjunctivitis, elevated CRP
Bhide *et al.* (2019)	38 y*	F	NR	No	Sepsis (COD), anemia, inguinal lymphadenopathy, low ejection fraction, hepatosplenomegaly, edema, elevated CRP, abnormal liver enzymes
Kilgallon *et al.* (2018)	13 y	M	NR	No	Anemia, abdominal pain, diarrhea, elevated ESR, positive antinuclear antibody
Xing *et al.* (2017)	43 y*	M	NR	No	Sepsis (COD), lymphopenia, elevated ALT
Alratrout *et al.* (2016)	8 y	M	NR	NR	Sepsis, microcytic anemia, arthralgia
Nofal *et al.* (2016)	9 y*	M	NR	Yes	Sepsis (COD), myocardial dysfunction, anemia, edema, leukocytosis, elevated ESR and CRP
Kreuter *et al.* (2016)	35 y	M	NR	NR	Arthralgia; myalgia; elevated CRP, LDH, and creatinine kinase
Bulur *et al.* (2015)	11 y	M	NR	No	Elevated ALT, AST, and CD19 B-cells; decreased serum IgG levels, CD3 T-cells, and CD4 T-cells
Griffith-Bauer *et al.* (2015)	6 y	M	NR	NR	NR
	7 y	M	NR	NR	NR
Lode *et al.* (2015)	20 m	M	NR	Yes	Thrombocytosis, elevated ESR and CRP
Shah *et al.* (2014)	20 y	M	NR	Yes	Leukocytosis, elevated ALT and AST
Uzoma *et al.* (2014)	18 yo.	M	NR	NR	Sepsis
	13 y	M	NR	NR	Anemia, elevated liver enzymes
Yamada *et al.* (2014)	7 y	M	NR	No	Sore throat, nasal congestion
Hervas *et al.* (2013)	9 y	M	VZV infection	NR	Myalgia, edema, ecchymosis, elevated CRP, hypoproteinemia
Lejuste *et al.* (2013)	64 y	F	Spider bite	NR	Frontal edema, headache, pruritus, elevated CRP
Luo *et al.* (2013)	15 y	F	NR	No	Leukocytosis, elevated serum globulin levels, hypoalbuminemia, decreased C3
Nanda *et al.* (2013)	12 y	M	Parvovirus B19 infection	Yes	Elevated CRP, ESR, ALT and AST
Oliveira *et al.* (2013)	33 y	M	NR	NR	NR
Rosman *et al.* (2013)	11 y	M	NR	NR	Abdominal pain, necrotizing vasculitis
Kaufman *et al.* (2012)	21 m	F	NR	Yes	Laryngeal edema causing difficulty breathing
	22 m	F	NR	No	NR
Lin *et al.* (2012)	10 y	M	NR	NR	Arthritis, elevated CRP
Meziane *et al.* (2012)	65 y*	F	NR	Yes	Acute respiratory disease with sepsis (COD), normochromic-normocytic anemia, lymphopenia, elevated CRP and ESR
Perrin *et al.* (2012)	34 m	M	NR	No	Hepatosplenomegaly
Harenberg *et al.* (2010)	30 y	M	NR	NR	Sepsis
Marenco *et al.* (2010)	23 y	M	NR	Yes	NR
Nassif *et al.* (2010)	49 y	M	NR	Yes	Myalgia, lymphopenia, hyponatremia, hypocalcemia
Zhang *et al.* (2010)	12 y	M	Measles vaccine	Yes	Bilateral interstitial pulmonary nodules, decreased albumin and LDH, elevated globulin and gammaglobulin
Helbling *et al.* (2009)	17 y	M	EBV infection	NR	Lymphadenopathy
Smith *et al.* (2009)	24 y	M	HSV-2 infection	NR	Elevated liver enzymes, increased C1q binding activity, S. aureus infections
Sotiriou *et al.* (2008)	20 y	F	NR	Yes	Myalgia, normochromic-normocytic anemia, elevated ESR and CRP
Kim *et al.* (2007)	8 y	M	NR	NR	Elevated CRP, ESR, and liver enzymes

Table 1. Summary of patient demographics and disease course. All patients had an associated fever even if no other systemic symptoms were reported.

Publication	Subject Age	Sex	Possible Etiology involvement	Mucosal	Systemic complications & abnormal labs
Pyrpasopoulou *et al.* (2007)	17 y	F	NR	NR	Anemia; diarrhea; elevated CRP, ESR, and transaminases; low serum albumin
Aydingoz *et al.* (2006)	37 y	M	NR	No	Obstructive and restrictive lung disease, leukocytosis, elevated ESR and liver enzymes
Helmbold *et al.* (2006)	20 y	M	NR	No	Lymphadenopathy, lymphocytosis Elevated liver enzymes
Malnar *et al.* (2006)	60 y*	M	NR	Yes	Intestinal and colon gangrene caused by thrombosis of superior mesenteric artery (COD), pulmonary thromboembolism, elevated liver enzymes
Aytekin *et al.* (2005)	27 y*	F	NR	NR	Sepsis (COD), anemia, elevated ESR and CRP, hyponatremia, hypercalcemia, hypoproteinemia
Herron *et al.* (2005)	8 y	F	NR	NR	Sepsis, acute respiratory distress syndrome, acute GI bleed, elevated IL-2
Tsianakas *et al.* (2005)	9 y	M	Nonfebrile enteritis	NR	Lymphadenopathy, elevated levels of serum TNF-α
Cozzio *et al.* (2004)	72 y*	NR	NR	NR	Sepsis (COD); bone marrow suppression with pancytopenia; and elevated CRP, IL-1, IL-4, IL-6, IL-8, IL-10
	26 y*	F	NR	NR	NR
Ito *et al.* (2003)	12 y	M	NR	NR	Anemia, microscopic hematuria, leukocytosis; prolonged PT and PTT; elevated fibrinogen, D-dimer, ESR, CRP, ALT, AST; hypoproteinemia; hypoalbuminemia; hyponatremia
Miyamoto *et al.* (2003)	76 y*	M	NR	NR	Hypovolemic shock (COD), elevated CRP and LDH
Rivera *et al.* (2003)	33 y	F	NR	Yes	Anemia, abdominal pain, elevated CRP
Yang *et al.* (2003)	14 y	M	EBV infection	Yes	Diarrhea, sore throat, nasal congestion
Yanaba *et al.* (2002)	21 y	M	NR	No	Sepsis, elevated CRP, hyponatremia, hypercalcemia, hypoproteinemia
Ricci *et al.* (2001)	10 y	F	EBV infection	No	Neutrophilia
Tsai *et al.* (2001)	45 y	M	CMV infection	Yes	Arthritis, pitting edema, elevated CRP, ESR, ALT, and AST; lymphocytosis; hypoalbuminemia
Puddu *et al.* (1997)	43 y*	F	NR	No	Cardiogenic shock (COD), leukocytosis; decreased C3 fraction; elevated ESR, CRP, platelets, ALP
Gungor *et al.* (1996)	59 y*	M	NR	No	Cardiac arrest (COD), alternating lymphopenia and lymphocytosis, alternating anemia and polycythemia, elevated ESR
Suarez *et al.* (1996)	32 y	M	NR	Yes	Weakness and impaired gait, elevated ALT and AST, hypoproteinemia, hypoalbuminemia
De Cuyper *et al.* (1994)	82 y*	F	NR	Yes	Pneumonia (COD); leukocytosis; hypogammaglobulinemia; hypoproteinemia; decreased CH50, C3, and C4; elevated LDH and 24-hour fecal fat
Fink-Puches *et al.* (1994)	16 y	M	NR	Yes	Elevated ESR, CRP, anti-streptolysin, and LDH
Lopez-Estebaranz *et al.* (1993)	18 y	M	NR	No	Elevated ESR and liver enzymes; leukocytosis
Luberti *et al.* (1991)	12 y	M	NR	No	Sepsis, arthritis, edema
Hoghton *et al.* (1989)	49 y*	F	NR	NR	Cardiogenic shock (COD), splenomegaly, anemia, lymphocytic myocarditis, pulmonary embolism, elevated ESR and reticulocytes
Nakamura *et al.* (1986)	21 y	M	NR	NR	Abnormal white blood cell count
Warshauer *et al.* (1983)	54 y	M	NR	Yes	Abdominal pain, lymphocytosis, eosinophilia, hypergammaglobulinemia
Auster *et al.* (1979)	7 y	F	Adenovirus type II infection	NR	Interstitial pneumonitis, leukocytosis
Burke *et al.* (1969)	15 y	M	NR	Yes	Lymphopenia; neutropenia; anemia; hypergammaglobulinemia; elevated anti-streptolysin; decreased polymorphonuclear leukocytes in bone marrow
	12 y	F	NR	No	Neutrophilia

*Fatal outcome reported. Alanine transaminase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), cause of death (COD), C-reactive protein (CRP), cytomegalovirus (CMV), erythrocyte sedimentation rate (ESR), Epstein-Barr virus (EBV), female (F), herpes simplex virus 2 (HSV-2), interleukin (IL), lactate dehydrogenase (LDH), male (M), months (m), tumor necrosis factor (TNF), not reported (NR), varicella zoster virus (VZV), years (y).

Eleven studies investigated the clonality of T-Cell Receptor (TCR) rearrangement in FUMHD of which three studies found no TCR rearrangement.[34,41,43] From the remaining eight studies, monoclonal TCR rearrangement was reported in five patients,[12,19,22,56] only one of which survived.[56] The age range of these five patients was 24-76 years old, with three patients being over 40 years old. Polyclonal TCR rearrangement was reported in four patients in the resolved cohort.[31,40,52,58] These patients ranged in age from 20 months old to 30 years old.

Sepsis was the most common cause of death in patients affecting 38.5% (5/13),[12-14,18,20,22] and cardiogenic shock affected 15.4% (2/13).[16,21] Other reported causes of death include cardiac arrest,[15] hypovolemic shock,[19] pneumonia,[5] and severe intestinal and colon gangrene.[17] The duration between symptom onset and hospitalization ranged from 1 week to 2 years.

Follow-up was reported for 45 patients and ranged from 2 weeks to 5 years. Among the 21 patients who developed recurrence of flares, 71.4% (15/21) were associated with the discontinuation of medication,[3,9,10,12,18,20,21,23,30,32,33,39,41-43,49,52,53,55,61,63] more specifically, 28.6% (6/21) were due to discontinuation of MTX.[9,10,30,41,49,52] Less commonly, recurrence was associated with administration of systemic corticosteroids, IVIG, or antibiotics in 14.3% (3/21) of patients.[3,55,61]

Treatment modalities

Treatment modalities used in each case are summarized in Tables 2 and 3. Reported topical treatments include topical corticosteroids, topical antibiotics, petrolatum, silver sulfadiazine, urea, and hypochlorous acid. Debridement is also commonly performed using whirlpool baths. Antibiotics were the most commonly used systemic treatment in the resolved cohort (73%, 40/55), followed by systemic steroid use in 73% (40/55) of patients. Systemic steroids were more commonly prescribed in the fatal group (85%, 11/13), followed by antibiotics in the fatal cohort (77%, 10/13). The most commonly prescribed medication for maintenance therapy was MTX. In these cases, antibiotics and/or systemic steroids were often used in conjunction with MTX for initial management.

Less commonly used treatments include antivirals, cyclosporine, biologics, IVIG, and phototherapy. Biologics were only used in three cases.[18,37,63] The most commonly used biologic was tumor necrosis factor-alpha (TNF-α) inhibitors,[18,37,63] while interleukin-6-receptor inhibitors and Janus kinase inhibitors were used in one case each.[63] In a patient with clinical resolution, tocilizumab, etanercept, and ruxolitinib were used for initial management, and ruxolitinib was continued for treatment of a flare.[63] Infliximab was used twice with resolution reported in one case[37] but fatality in the other case.[18] Several types of phototherapies were used including psoralen ultraviolet A phototherapy (PUVA), narrowband ultraviolet B phototherapy (NBUVB), photoimmunotherapy, and extracorporeal phototherapy. The most commonly used phototherapy was NBUVB, which was used in four cases,[5,33,45,57] followed by PUVA, which was used in two cases.[12,41] In both treatment modalities, one case was fatal. Photoimmunotherapy[16] and extracorporeal phototherapy[43] were used in one case each, with the former resulting in fatality despite treatment.

Adverse effects

Out of the 68 total patients, eight patients (12%, 8/68) experienced adverse effects from treatment.[9,12,18,39,45,54,58,59] MTX was attributed to cause the most adverse effects, affecting six patients, including: nausea, pancytopenia, renal insufficiency, acute elevation of serum transaminases, liver enzyme deterioration, bone marrow suppression, periportal fibrosis, and hepatic inflammatory changes.[9,12,18,39,45,54] The other reported adverse effects include anaphylactic reactions,[45] gastrointestinal discomfort,[59] and increased urine calcium levels with related formation of bilateral kidney stones[58] attributed to IVIG, pentoxifylline, and systemic steroid use, respectively. None of these adverse effects were considered unexpected with the treatments given.

Quality and risk of bias

Quality assessment scores ranged from 9-18 (Table 4). Two publications attained an ideal score of 18.[9,39] The majority of publications did not report if patients experienced adverse effects related to treatment. Out of the 10 publications that reported adverse effects, three publications failed to provide an adequate report by not reporting adverse effects for all the patients presented.[9,12,18,20,26,39,45,54,58,59] Another criterion for poor performance was follow-up period. Only 42 publications reported any follow-up period, and 22 publications failed to follow patients for at least 9 months. All publications reported information for the seven other criteria.

Discussion

FUMHD is a rare form of PLEVA with a rapid and potentially fatal course. While most cases that resulted in resolution were quickly diagnosed and treated, the majority of cases that had fatal outcomes were not treated for greater than 1 month. Therefore, early diagnosis and treatment may be crucial in management of FUMHD, but the absence of definite diagnostic criteria and therapeutic protocols presents barriers to timely management.

Diagnostic challenges of FUMHD

The challenges of FUMHD management revolve primarily around its diagnosis due to a lack of specific laboratory and histopathology findings.[8] Nonspecific laboratory findings usually include elevated inflammatory markers, anemia, abnormal lymphocyte count, and abnormal liver enzymes. Similarly, histopathological findings usually include the typical features of PLEVA or vasculitis, adding to the difficulty of diagnosing this rare disease.

Several case reports demonstrate the potential for initial misdiagnosis as other conditions, including: Stevens-Johnson Syndrome (SJS),[8] presumed pustular psoriasis,[47] Kawasaki disease,[62] and most commonly chickenpox.[9,10] Although FUMHD can be managed with similar treatments to other conditions such as SJS and Kawasaki disease, accurate diagnosis allows for more targeted management which may improve treatment outcomes.

Moreover, eight cases of PLEVA identified to have progressed to FUMHD during the course of hospitalization have been reported in literature.[22,23,33,39,41,58,65,67] Healthcare providers may consider this potential progression if patients start to present with symptoms of FUMHD. A delay in treatment may contribute to the development of potentially devastating systemic manifestations.

A key challenge in recognizing the development of FUMHD is the absence of set diagnostic criteria. Nofal *et al.* have proposed the following diagnostic criteria: acute onset of generalized ulceronecrotic papules and plaques associated with a fever, a rapidly progressive course that does not resolve spontaneously, and histopathological findings consistent with PLEVA.[7] This systematic review found a majority of patients presented with features that met the criteria suggested by Nofal *et al.*[7] FUMHD

Table 2. Summary of treatment modalities used in each case in the resolved cohort. A treatment was considered unsuccessful if it did not show clinical improvement and the authors switched to a different treatment.

Publication	Age	Antibiotic	Antiviral	Steroids	MTX	CYA	Biologic	IVIG	Phototherapy	Other Treatments
Blohm *et al.* (2021)	13 y	+						+		Topical urea
Ngo *et al.* (2021)	43 y	+		+	+/M	+				
Wu *et al.* (2021)	7 y				+	X	+			
Schaan de Souza *et al.* (2020)	NR	+		+	X	+		+		
Wang *et al.* (2020)	11 y	X		X	+					Double filtration plasmapheresis was ineffective. Lymphoplasmapheresis showed improvement.
Weins *et al.* (2020)	9 m			+	+					
Kilgallon *et al.* (2018)	13 y	+		+	+/M					
Alratrout *et al.* (2016)	8 y	+		+	+					
Kreuter *et al.* (2016)	35 y			X	X		+			
Bulur *et al.* (2015)	11 y	X		+	+					
Griffith-Bauer *et al.* (2015)	6 y 7 y	X +		X	+ +					
Lode *et al.* (2015)	20 m			+		+				
Shah *et al.* (2014)	20 y	+		+	+/M					
Uzoma *et al.* (2014)	18 y 13 y	X +				 +			 +	Pentoxifylline Pentoxifylline
Yamada *et al.* (2014)	7 y	X		+						Potassium iodide was ineffective.
Hervas *et al.* (2013)	9 y	+	+	+					+	Human serum albumin and topical zinc sulfate
Lejuste *et al.* (2013)	64 y			+						
Luo *et al.* (2013)	15 y			+	+					
Nanda *et al.* (2013)	12 y	+		+	X			X	+	
Oliveira *et al.* (2013)	33 y	+								
Rosman *et al.* (2013)	11 y	+		+	+					Whirlpool baths and cyclophosphamide
Kaufman *et al.* (2012)	21 m 22 m			 +	+/M +/M					
Lin *et al.* (2012)	10 y			+	+/M					
Perrin *et al.* (2012)	34 m	+	+	+	+/M			+		
Harenberg *et al.* (2010)	30 y	+	X	+	X					Suprathel, Aquacell, and polyhexanide solution
Marenco *et al.* (2010)	23 y			+	+/M			+	+	
Nassif *et al.* (2010)	49 y			+						
Zhang *et al.* (2010)	12 y	X		+/M	+/M					
Helbling *et al.* (2009)	17 y				+					
Smith *et al.* (2009)	24 y	+	+							Potassium permanganate baths
Sotiriou *et al.* (2008)	20 y	+		+	+/M					High-calorie parenteral therapy, whirlpool and permanganate baths
Kim *et al.* (2007)	8 y	+		+		+				hPDGF and DuoDerm dressings
Pyrpasopoulou *et al.* (2007)	17 y	+	X	+/M	+/M			+		Potassium permanganate baths
Aydingoz *et al.* (2006)	37 y	+		+						
Helmbold *et al.* (2006)	20 y	X	+	X						
Herron *et al.* (2005)	8 y	+			+/M	+				
Tsianakas *et al.* (2005)	9 y	+		+	+					
Ito *et al.* (2003)	12 y	+		+/M	+	X				Topical tocoretinate ointment
Rivera *et al.* (2003)	33 y			+	+					
Yanaba *et al.* (2002)	21 y	+		+				+		Serum albumin, FFP, cultured epidermal autografts and meshed allografts of cadaver skin
Yang *et al.* (2002)	14 y	+		+						
Ricci *et al.* (2001)	10 y									
Tsai *et al.* (2001)	45 y	+	X						+	
Suarez *et al.* (1996)	32 y	+		+	+					Whirlpool baths
Fink-Punches *et al.* (1994)	16 y	+		+	+					
Lopez-Estebaranz *et al.* (1993)	18 y	+		+	+/M				+	Whirlpool baths
Luberti *et al.* (1991)	12 y	+/M	X	X						Whirlpool baths
Nakamura *et al.* (1986)	21 y	+								
Warshauer *et al.* (1983)	54 y	+		+	X					Thiabendazole did not suppress flares
Auster *et al.* (1979)	7 y	+								
Burke *et al.* (1969)	15 y 12 y	+		 +						Whole blood, pooled plasma, albumin, γ-globulin, and whirlpool baths Whirlpool baths

Cyclosporine (CYA), fresh frozen plasma (FFP), human platelet derived growth factor (hPDGF), intravenous immunoglobulin (IVIG), maintenance treatment (M), methotrexate (MTX), months (m), successful treatment (+), unsuccessful treatment (X), years (y).

is a potential differential diagnosis in patients with ulceronecrotic papules and plaques associated with a fever and should be ruled out due to its fatal course.

Risk factors for poor prognosis

Systemic and mucosal involvement

Blohm *et al.* suggested a mortality risk score based on increased age, systemic involvement, and mucosal involvement increasing the mortality risk.[11] Although increased age and systemic involvement is related to increased risk of mortality in this systematic review, mucosal involvement did not appear to be associated with mortality risk and was proportionally reported in the resolved and fatal group.

Age

The majority of fatal cases affected patients over the age of 40 years old. While it is unclear whether advanced age is a potential risk factor that may lead to a fatal outcome, it should be noted that most patients over 40 years were admitted at least 3 weeks after onset of symptoms. The delay in diagnosis and treatment may have played a role in the fatal outcome of these cases since the common cause of death was a form of infection or shock, which may take time to develop a fatal course.[14,20,22] Particularly in immunocompromised patients or those with advanced age, early treatment may prevent this potentially fatal sequelae.

TCR Rearrangement

Another feature to consider for a mortality risk score is clonality of TCR rearrangement. All cases that reported polyclonal TCR rearrangement resulted in disease resolution,[31,40,52,58] while most cases with monoclonal TCR rearrangement were associated with mortality,[12,19,22] except in one case where the TCR rearrangement was mild and the patient experience disease resolution.[56] The type of TCR rearrangement may be related to age as polyclonal TCR rearrangement was associated with younger patients, while monoclonal TCR rearrangement was generally associated with older patients. As a result, the mortality risk score suggested by Blohm *et al.* may already incorporate TCR rearrangement, as age is a factor in the calculation.[11] However, it seems that the degree of monoclonal TCR rearrangement is more important than patient age as a 26-year-old patient succumbed to the disease,[12] while another 24-year-old patient with only mild monoclonal TCR rearrangement was able to recover.[56]

In patients with recurrent FUMHD, flares often occurred after discontinuation of treatment, most commonly MTX.[9,10,30,41,49,52] In some of these cases, patients required continued treatment even after resolution of symptoms and hospital discharge to prevent recurrence, although, the authors do not specify how long patients continued maintenance treatment in most cases.[8,10,11,32,34,35,39,41-43,49,50,55,67] Clinicians should be aware of the potential for recurrence with discontinuation of treatment and future studies may help better determine when to use longer maintenance of MTX, in addition to the administration of antibiotics for the treatment of skin infections, to prevent the likelihood of relapse.

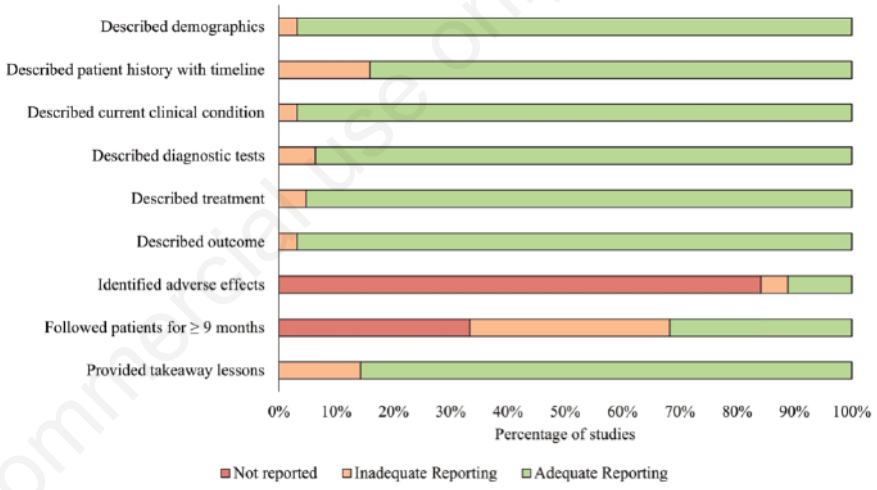

Figure 2. Scores for each criterion of quality presented as percentages across all included studies.

Table 3. Summary of treatment modalities used in each case in the fatal cohort.

Publication	Age	Antibiotic	Antiviral	Steroids	MTX	CYA	Biologic	IVIG	Phototherapy	Other Treatments
Bhide *et al.* (2019)	38 y	+		+	+					
Xing *et al.* (2017)	43 y	+		+				+		
Nofal *et al.* (2016)	9 y	+		+		+		+		
Meziane *et al.* (2012)	65 y		+	+	+		+	+		
Malnar *et al.* (2006)	60 y	+		+						
Aytekin *et al.* (2005)	27 y	+	+	+				+		FFP and a high-calorie parenteral therapy
Cozzio *et al.* (2004)	72 y				+			+		
	26 y			+	+				+	
Miyamoto *et al.* (2003)	76 y	+								
Puddu *et al.* (1997)	43 y	+		+						
Gungor *et al.* (1996)	52 y	+		+	+					
De Cuyper *et al.* (1994)	82 y	+		+					+	
Hoghton *et al.* (1989)	49 y	+	+	+	+				+	

Attempted treatments (+), cyclosporine (CYA), fresh frozen plasma (FFP), intravenous immunoglobulins (IVIG), maintenance treatment (M), methotrexate (MTX) months (m), years (y).

Table 4. Quality Assessment (Ideal Score = 18).

Publication	Total Score
Wu *et al*. (2021)	15
Blohm *et al*. (2021)	15
Ngo *et al*. (2021)	14
Schaan de Souza *et al*. (2020)	17
Wang *et al*. (2020)	14
Weins *et al*. (2020)	16
Bhide *et al*. (2019)	14
Kilgallon *et al*. (2018)	15
Xing *et al*. (2017)	14
Alratrout *et al*. (2016)	16
Kreuter *et al*. (2016)	15
Nofal *et al*. (2016)	15
Griffith-Bauer *et al*. (2015)	15
Bulur *et al*. (2015)	17
Lode *et al*. (2015)	16
Shah *et al*. (2014)	15
Yamada *et al*. (2014)	16
Uzoma *et al*. (2014)	17
Lejuste *et al*. (2013)	15
Luo *et al*. (2013)	16
Nanda *et al*. (2013)	17
Oliveira *et al*. (2013)	16
Hervas *et al*. (2013)	14
Rosman *et al*. (2013)	16
Kaufman *et al*. (2012)	14
Perrin *et al*. (2012)	14
Meziane *et al*. (2012)	17
Lin *et al*. (2012)	18
Nassif *et al*. (2010)	14
Harenberg *et al*. (2010)	11
Marenco *et al*. (2010)	14
Zhang *et al*. (2010)	14
Helbling *et al*. (2009)	15
Smith *et al*. (2009)	15
Sotiriou *et al*. (2008)	16
Kim *et al*. (2007)	14
Pyrpasopoulou *et al*. (2007)	12
Aydingoz *et al*. (2006)	15
Helmbold *et al*. (2006)	14
Malnar *et al*. (2006)	14
Aytekin *et al*. (2005)	13
Herron *et al*. (2005)	14
Tsianakas *et al*. (2005)	17
Cozzio *et al*. (2004)	9
Ito *et al*. (2003)	15
Miyamoto *et al*. (2003)	13
Rivera *et al*. (2003)	15
Yang *et al*. (2002)	16
Yanaba *et al*. (2002)	14
Ricci *et al*. (2001)	15
Tsai *et al*. (2001)	15
Puddu *et al*. (1997)	14
Gungor *et al*. (1996)	14
Suarez *et al*. (1996)	18
De Cuyper *et al*. (1994)	13
Fink-Punches *et al*. (1994)	14
Lopez-Estebaranz *et al*. (1993)	15
Luberti *et al*. (1991)	15
Hoghton *et al*. (1989)	14
Nakamura *et al*. (1986)	14
Warshauer *et al*. (1983)	13
Auster *et al*. (1979)	13
Burke *et al*. (1969)	15

Potential therapeutic efficacy of treatment modalities

Successful treatment modalities may be targeting the potential immune-mediated etiology of FUMHD. The most commonly used treatments in the resolved cohort include antibiotics, systemic steroids, and MTX, with MTX commonly prescribed to prevent flares. The effect of successful treatment modalities on the immune system may underlie their success. Although the exact etiology of FUMHD remains unclear, studies suggest that it is immune-mediated and may either be a cytotoxic attack on altered epidermal antigens[65] or a clonal T-cell cutaneous lymphocytic disorder.[12,19,68]

MTX suppresses T-cell activation and inhibits cell proliferation, which would allow it to prevent a cytotoxic attack or to halt proliferation of monoclonal T-cells, respectively.[69] The medication's mechanism of action affects both of the potential mechanisms of pathogenesis, which may underlie its effectiveness in treating FUMHD. Other successful treatment modalities may work through similar mechanisms. Tetracycline,[70] pentoxifylline,[71] and dapsone,[72] have anti-inflammatory properties, and systemic steroids have immunosuppressive effects similar to MTX.[73]

Biologics are a potential targeted treatment for FUMHD that may serve as an alternative to high-dose immunosuppressive therapy. Several studies have found increased levels of interleukins and TNF-α in patients with FUMHD,[12,58,63] and several cases have used biologics to successfully treat FUMHD.[37,63]

Although FUMHD is associated with an infectious trigger in some cases, treatment of the infection was not always vital to successful resolution of FUMHD. In a case of FUMHD with probable CMV trigger, initial treatment with intravenous acyclovir did not allow for complete resolution and further treatment with tetracycline and NBUVB were necessary.[57] This suggests the potential benefit of targeting the immune response mediating the pathogenesis of FUMHD even in cases with infectious etiology.

Quality of current literature

Although the overall quality of studies in this systematic review was adequate (Figure 2), a majority of studies lacked detail in describing the disease course and sufficient follow-up. The disease course was not adequately reported in ten cases.[5,12,18,25,27,29,31,43,49,50] These cases failed to mention the length of time from initial development of lesions to initial treatment. Due to the rapid progression of FUMHD, a more detailed history throughout studies would help clinicians better understand how the disease initially presents and the progression of the disease, potentially allowing more rapid identification of FUMHD as a potential differential diagnosis since it often presents similarly to other diseases.

Based on the average time to recurrence reported in a previous systematic review on PLEVA, studies should follow patients for at least 9 months to accurately represent the likelihood of recurrence and to report any potential risk factors or triggers for flares. This may allow clinicians to better understand which patients are at risk, to take adequate preventative measurements, and to monitor these patients closely for recurrence.

Currently, the only published reports of FUMHD are case reports, often with only one patient, which makes it difficult to define characteristics of FUMHD and the most effective treatments. Due to the rare and potentially fatal nature of this disease, large prospective studies may not be feasible, but the literature would benefit from case reports with longer follow-up periods and larger retrospective studies to help increase the understanding of FUMHD.

Conclusions

The current literature supports the use of multiple treatments for FUMHD including MTX, systemic steroids, antibiotics, antivirals, IVIG, biologics, cyclophosphamide, CYA, pentoxifylline, and phototherapy. Systemic steroids and antibiotics are the most commonly used initial treatments, and MTX is most commonly used for maintenance therapy to prevent recurrence. Newer treatments, such as biologics, have shown potential for both initial treatment and maintenance therapy. The absence of definite diagnostic criteria and therapeutic protocols underlines the difficulty that physicians face when it comes to diagnosing and treating FUMHD. Future reports with adequate follow-up periods and larger, well-designed studies may further establish defined diagnostic criteria and optimum treatment regimens.

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