A Case Report of Febrile Ulceronecrotic Mucha-Habermann Disease in Thailand.

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ABSTRACT:

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Febrile ulceronecrotic Mucha-Habermann disease (FUMHD) is a rare severe variant of pityriasis lichenoides et varioliformis acuta (PLEVA) characterized by an acute onset of ulceronecrotic papules, rapidly coalescing into large necrotic ulcers and associated with high fever, severe systemic symptoms with a reported mortality rate approximately 20%. We reported a case of a 39-year-old man with a FUMHD and transaminitis. He was treated with prednisolone, tetracycline, dapsone, and narrowband UVB (NB-UVB) phototherapy without disease controlled. FUMHD has been reported with abnormally high serum levels of TNFα and cyclosporine is an immunosuppressive agent that suppresses interleukin-2 and TNFα production. The patient had favorable response after 3 months of cyclosporine therapy.

Key Words: Febrile ulceronecrotic Mucha-Habermann disease, tetracycline, cyclosporine

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บทคัดย่อ:

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สถาบันโรคผิวหนัง กรมการแพทย์ กระทรวงสาธารณสุข

Febrile ulceronecrotic Mucha-Habermann disease (FUMHD) เป็น variant ของโรค pityriasis lichenoides et varioliformis acuta (PLEVA) ที่มีความรุนแรง โดยมีลักษณะผื่นตุ่มนูนแดงที่แตกเป็นแผลอย่างรวดเร็ว มีอาการไข้ร่วมกับอาการทางระบบต่างๆ เช่น ตับอักเสบ ปอดอักเสบ กล้ามเนื้อหัวใจอักเสบ อาการทางระบบประสาท เป็นต้น และยังมีอัตราการเสียชีวิตสูงถึงร้อยละ 20 รายงานฉบับนี้เป็นการนำเสนอผู้ป่วยชายอายุ 39 ปี ที่มีอาการ FUMHD ร่วมกับตับอักเสบ โดยได้รับการรักษาด้วยยา prednisolone, tetracycline, dapsone และรักษาด้วยการฉายแสง narrowband UVB แต่พบว่ายังไม่สามารถควบคุมอาการของโรคได้ FUMHD มีรายงานว่ามีความเกี่ยวข้องกับปริมาณ TNFα ที่สูงขึ้น cyclosporine เป็นยากดภูมิคุ้มกัน โดยสามารถลดระดับ IL-2 และ ลดปริมาณการสร้าง TNFα ได้นำมาใช้ในการรักษาผู้ป่วย ซึ่งพบว่าผู้ป่วยตอบสนองดีต่อการรักษาด้วยยา cyclosporine หลังจากได้รับการรักษาเป็นเวลา 3 เดือน

คำสำคัญ: Febrile ulceronecrotic Mucha-Habermann disease, tetracycline, cyclosporine

Introduction

Pityriasis lichenoides et varioliformis acuta (PLEVA) is an inflammatory skin disease characterized by an acute onset of ulceronecrotic papules, rapidly coalesced into large necrotic ulcer. Febrile ulceronecrotic Mucha-Habermann disease (FUMHD) is the more severe ulcerative variant of PLEVA associated with high fever and severe systemic symptom with a reported mortality rate of approximately 20%. We reported a case of difficult to treat FUMHD with transaminitis.

Case Report

A 39-year-old man presented with fever, malaise accompanied with multiple erythematous papules on his face, neck, trunk, both arms, and legs for 2 weeks, and rapidly progress to necrotic ulcer. During the admission, physical examination revealed body temperature 39°C. There were multiple diffuse scaly erythematous papules, some ulceronecrotic papules and plaques with erythematous round erosions on face, neck, trunk, and the upper and lower extremities which involved 60% of body surface area (Fig.1). The palms, soles, scalp, nail and oral mucosa were spared.

The laboratory test showed leukocytosis with neutrophils predominated (WBC 13,400 cell/mm^3, PMN 77%) and transaminitis (AST 100 U/L, ALT 153 U/L). There were negative study of the serology test for Hepatitis B,C and Herpes simplex virus. Rapid plasma reagent (RPR) test

and Human immunodeficiency virus (HIV) antibody were all negative. The titers of Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) IgG antibodies were 1:3200 and > 1:2560 respectively. The Chest x-ray, electrocardiogram (EKG), and ultrasound examination of upper abdomen were unremarkable.

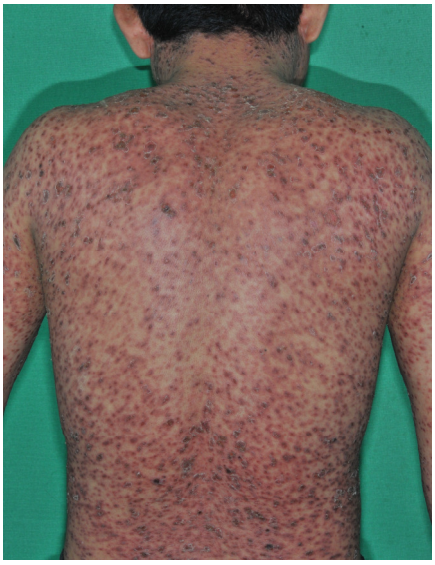

Fig. 1 Multiple diffuse ulceronecrotic papules on the back and upper extremities some with central crust.

The histopathological examinations showed focal parakeratosis with focal interface vacuolar change and scatter necrotic keratinocytes in the epidermis. The dermis exhibited a superficial and deep perivascular lymphocytic infiltration without vasculitis change (Fig.2). These findings confirmed the diagnosis of PLEVA.

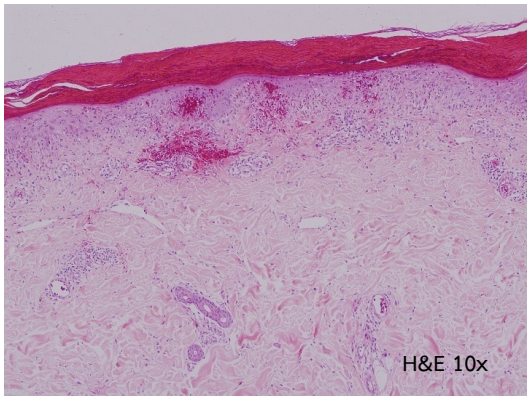

Fig. 2 The histological exam showed focal parakeratosis, focal interface change with necrotic keratinocytes, superficial and deep perivascular lymphocytic infiltration. (10x)

FUMHD was diagnosed based on clinicopathological correlation. The treatment was started with tetracycline 2 g/day and prednisolone 60 mg/day (1 mg/kg/day). The lesions rapidly cleared after 10 days. Two-weeks later, severe transaminitis was detected, probably caused by tetracycline. For this reason, tetracycline was discontinued and changed to dapsone 100 mg/day combined with prednisolone 60 mg/day and NB-UVB phototherapy. After gradually tapered off prednisolone over a period of 3 months, the skin lesions eventually flared up without presenting of fever and transaminitis. The dosage of oral prednisolone was increased to 30 mg/day with initiation of cyclosporine 100 mg/day (1.4 mg/kg/day). Dapsone and NBUVB phototherapy were withdrawal. The disease was controlled

after 3 months with cyclosporine 100 mg/day and prednisolone can be tapered off without forming new lesion at the current (Fig.3).

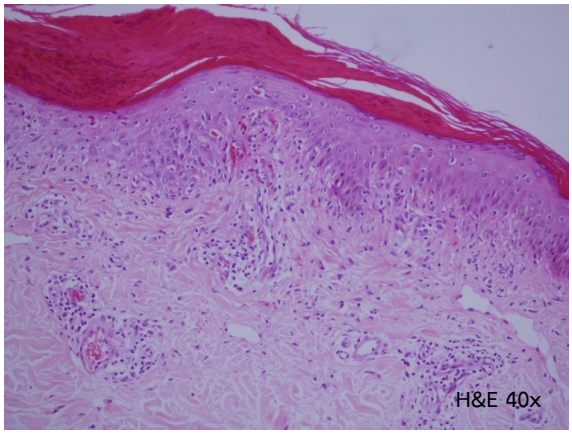

Fig. 3 The histological exam showed focal parakeratosis, focal interface change with necrotic keratinocytes, superficial and deep perivascular lymphocytic infiltration. (40x)

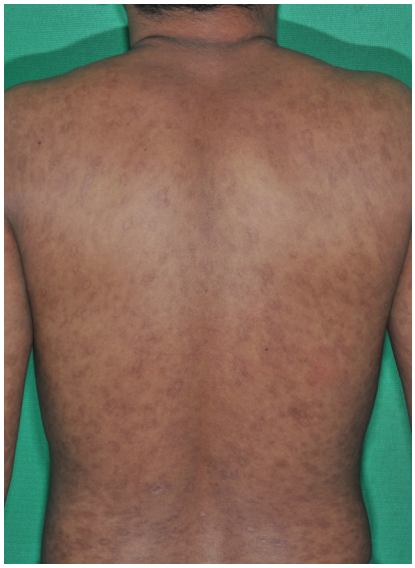

Fig. 4 Healing of cutaneous lesion after 3 months of cyclosporine therapy with post inflammatory hyperpigmentation.

Discussion

Febrile ulceronecrotic Mucha-Habermann disease (FUMHD), is a severe ulcerative variant of pityriasis lichenoides et varioliformis acuta (PLEVA), characterized by an acute onset of ulceronecrotic papules, rapidly coalescing into large necrotic ulcers. The associations with high-grade fever and severe systemic symptoms including liver dysfunction, abdominal pain, interstitial pneumonitis, lymphocytic myocarditis, central nervous system involvements such as stupor or agitation, pancytopenia, diffuse intravascular coagulation and rheumatologic manifestation have been reported.[1-3]

FUMHD can occur in children and young adults but mainly in the second and third decades of life, and predominantly in men. The mean age of patients in the reported cases is 27 years old.[2] In general, the disease progresses in weeks or months, but can evolve into a chronic disease with exacerbation and remission.[4] The mortality rate of FUMHD is approximately 20% and reported cases were due to pulmonary thromboembolism, sepsis, hypovolemic shock, and thrombosis of superior mesenteric artery.[2] Children tend to have more favorable prognosis with no reported cases of death.[2]

The exact pathogenesis of FUMHD is unknown. There are three possible theories to explain the pathogenesis of PLEVA: firstly, an inflammatory reaction triggered by infectious

agents for which several pathogens have been proposed such as EBV, adenovirus, CMV, parvovirus B19, varicella zoster virus and HIV-1; secondly, an immunological process might be the pathogenesis. Yanaba *et al.* observed predominantly cytotoxic $CD8^+$ lymphocytes infiltrate around the dermis and epidermis.[5] The elevation of soluble IL-2 receptor level and high serum levels of TNFα have been observed in FUMHD;[6,7] and lastly, hypersensitivity vasculitis mediated by immune complexes.[1]

The laboratory tests are not specific and may show markers of inflammation such as raised erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), increase of leukocytes, liver enzymes and lactate dehydrogenase (LDH), anemia, and hypoproteinemia.[8] There may also be serological evidence of associated viral infection such as CMV or EBV.[9, 10]

In FUMHD or PLEVA, histopathology reveals focal parakeratosis often associated with scales crust. There are necrotic keratinocytes over the epidermis with lymphocytes exocytosis. The basal layer is vacuolated. The superficial dermis is edematous and diffuse lichenoid inflammatory infiltrate with extravasation of red blood cells. The middle and deep dermis are also involved, and often associated with variable leukocytoclastic vasculitis.[8, 11] The immunohistochemical studies indicate the proportion of CD8 T cells that predominates in the PLEVA and CD4 T cells predominate in the pityriasis lichenoides chronica (PLC).

In the literature, there are several treatment modalities that had been described but due to the small number of cases and uncertained etiology, it is difficult to evaluate a specific treatment.

Case reports of FUMHD had recommended high-dose immunosuppressive therapy in combination with antibiotics or acyclovir.[12] The use of high dose of oral corticosteroids is initially to reduce the inflammatory component, followed by oral antibiotics for maintenance.[4] Several authors have published cases of complete healing with the use of tetracycline or erythromycin.[1, 13, 14] The efficiency can range from complete remission to no improvement.[8] The best result has been related to erythromycin for children and tetracycline has been reported as first-line treatment in adults.[1]

Immunosuppressive monotherapy with methotrexate or cyclosporine or a combination of these drugs with a high dose of glucocorticoids has been used in several cases.[11, 15, 16] Tsianakas and Hoeger reported the clinical and histopathologic transition from PLEVA to FUMHD has been associated with abnormally high serum levels of TNFα.[7] Cyclosporine is an immunosuppressive agent that suppresses interleukin-2 and TNFα production. The use of oral cyclosporine with an initial dose of 2.5

mg/kg/day then subsequently tapered to 1.25 mg/kg/day has been mentioned good results in an 8-year-old patient with FUMHD. Moreover, Yeom *et al.* reported a 59-year-old patient from Korea with FUMHD successfully treated with oral cyclosporine.[17,18] Additional advantages of cyclosporine are corticosteroids sparing effect, rapid control of fulminant symptoms, and low toxicity compared to methotrexate especially in children.

The efficient use of dapsone, pentoxifylline and phototherapy with ultraviolet light A or B as well as psoralen with UVA (PUVA) therapy had been described.[8, 19]

The anti-TNFα treatment such as infliximab should be considered as a treatment option.[2] IVIG could play a role as an adjunctive therapy in association with TNFα inhibitors or immunosuppressive therapy.[20] Some cases with substantial skin necrosis necessitate surgical debridement with skin graft.

Our patient had been treated with tetracycline 2 g/day and prednisolone 60 mg/day (1mg/kg/day). The lesions rapidly cleared after 10 days. Two-weeks later, severe transaminitis was detected, probably caused by tetracycline. For this reason, tetracycline was discontinued and changed to dapsone 100 mg/day accompanied with NB-UVB phototherapy. Nevertheless, the disease flared up after tapered off prednisolone. Treatment was then changed to cyclosporine 100 mg/day combined with prednisolone 30 mg/day. The disease was well control after 3 months of treatments and prednisolone can now be tapered off without forming a new lesion.

In conclusion, FUMHD is a rare and severe ulcerative variant of PLEVA. Early diagnosis and appropriate treatment is important. Several modalities of treatment options have been mentioned with variable results. We reported the case of FUMHD with transaminitis and had favorable outcome with cyclosporine.

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