

Necrolytic Acral Erythema

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Abstract

Background: Necrolytic acral erythema (NAE) is a rare dermatosis which has been regarded as an early cutaneous marker of hepatitis C virus infection. The clinical manifestation of NAE is similar to necrolytic migratory erythema, psoriasis and tinea corporis. The difference is that the patients with NAE also suffer from hepatitis C virus infection.

Case: A 59 year old woman came and complained about itchy erythematous-violaceous plaques since a year ago. The patient has a history of hepatitis C infection since 2 years ago. On the superior and inferior extremities region, there were erythematous-violaceous plaques with partially hyperpigmentation with well-demarcated border, multiple discrete with thin scales and lichenification. Histopathological examination of the lesion obtained psoriasiform, hyperkeratosis, neutrophilic microabscess, epidermal necrosis, spongiosis and infiltration of inflammatory cells in the epidermis.

Discussion: Necrolytic acral erythema has been reported exclusively in patients with hepatitis C and is thought to be pathognomonic of this infection. Acute lesions often show erythema with vesicles and flaccid bullae. Chronic lesions appear as erythematous to violaceous plaques with thick scales, erosions and crust. Acral sites are predominantly involved. The histopathological examination shows psoriasiform hyperplasia epidermal, neutrophilic microabscesses, dilatation of small vessels, parakeratosis and infiltration of inflammatory cells. In this case, the physical and histopathological examination support the diagnosis of NAE.

Keywords: Hepatitis c, necrolytic acral erythema.

Introduction

Hepatitis C virus (HCV) is a type of ribonucleic acid (RNA) virus with 6 major genotypes. This virus is responsible for acute and chronic hepatitis, cirrhosis, and liver cancer [1]. The World Health Organization (WHO) estimated that around 170 million people in the world is infected with hepatitis C. This virus is considered a global health problem, because of its prevalence of intra and extra hepatic features. About 85% of the cases developed into chronic hepatitis. Chronic hepatitis C viral infection often shows varied difference of clinical spectrum, from asymptomatic with normal enzyme level to severe active chronic hepatitis. Therefore, early diagnosis is mandatory [2]. A recent study showed that around 70-74% cases manifest to extra hepatic features [3].

Extra hepatic manifestations of HCV infection include abnormalities of the blood, skin, and kidney, autoimmune manifestation, and abnormalities of the nervous system, endocrine, cardiovascular and respiratory [1]. Skin is the main target of extra hepatic feature of HCV infection. There are some factors causing the HCV-related skin abnormalities, such as viral, genetic, and environmental factors.

In most cases, the mechanisms which triggers or worsens the skin manifestations of HCV infection are still unknown and further examination is needed [4]. Some of the dermatological features of HCV infection are: mixed cryoglobulinemia, polyarteritis nodosa (PAN), necrolytic acral erythema (NAE), red finger syndrome, porfria cutanea tarda, puritus, and planus lichen [5]. Beside that, other dermatological features caused by HCV are: urticaria, vasculitis urticaria, and multiform erythema [6].

Necrolytic acral erythema (NAE) was first described by el Darouti et al in 1996 [7-12]. Necrolytic acral erythema (NAE) is a rare skin condition in hepatitis C patients and is thought to be related to zinc deficiency, although the mechanism is unclear. This problem has been reported in around the world, such as Pakistan, India, and the United States with the majority of cases was found in Egypt. It may be related to the higher prevalence of hepatitis C in Egypt (more than 20%) than other places in the world (3%). One cohort study showed that the prevalence of NAE in hepatitis C patients is around 1.7% [13].

The etiology of NAE is multi factorial and liver dysfunction is known to be related to the development of the disease. Very little

information has been provided about the history, prevalence, and clinical features of NAE [14].

Case

A 59 years old woman came to the Dermatovenereology Outpatient Clinic of Moewardi General Hospital Surakarta Indonesia and complained about painless, itchy, erythematous-violaceous plaques on her hands and legs since 1 year ago. At first, she complained about vesicles filled with fluid and erythematous plaques, but then the vesicles ruptured. Then the plaques became violaceous accompanied with thin scales. The symptoms occurred after the patient was infected with hepatitis C virus 2 years ago. The patient also suffered from diabetes since 5 months ago and she already got the medications for her diabetes from Internal Medicine Clinic of Moewardi General Hospital. The physical examination revealed normal range, on the superior and inferior extremities we found erythematous-violaceous plaques with hyperpigmentation and well-demarcated border, discrete, and lichenified with thin scales (**Figure 1**).



Figure 1: (A-F) Superior and inferior extremities showed erythematous-violaceous plaques with hyperpigmentation, multiple, discrete, lichenified with thin scales.

From the laboratory findings we found that increased of AST level was 164 U/L (normal range: 5-40 U/L), ALT level was 120 U/L (normal range: 5-41 U/L), total bilirubin level was 4.00 (normal range: <1.1 mg/dl) and direct bilirubin level was 3.00 (normal range: < 0.3 mg/dl). We also found antibody anti-HCV reactivity with enzyme-linked immunosorbent assay (ELISA) technique. Abdominal contrasted MSCT scan demonstrated liver enlargement. The skin scraping examination with 10% KOH was negative. The histopathological examination using hematoxylin eosin (HE) staining showed psoriasiform, hyperkeratosis, neutrophilic microabscess, epidermal and spongiosum necrosis, with inflammatory cell infiltration, supporting the diagnosis of NAE (**Figure 2**).

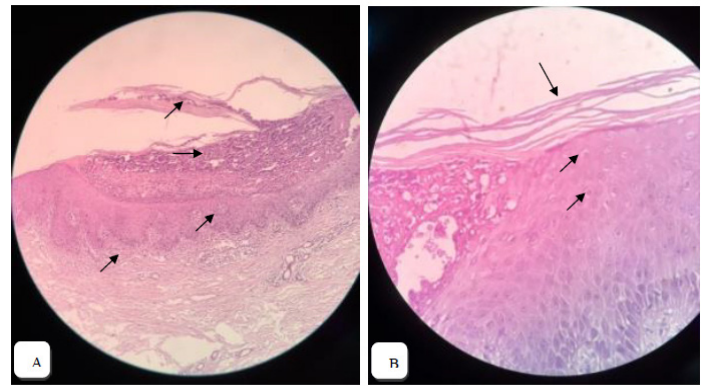


Figure 2: (A) Histopathology examination using HE staining with 10x magnification shows psoriasiform image, neutrophilic microabscess, epidermal necrosis, and inflammatory cells infiltration. (B) With 40x magnification we found hyperkeratosis and spongiosis.

From the Internal Medicine Department, this patient has given therapies which are 200 mg Curcuma[®] once daily, 300 mg UDCA[®] twice daily, B complex vitamin once daily, and Novorapid[®] injection 10-10-8. From the Dermato-venereology Clinic she was given Methylprednisolone 20 mg daily, Cetirizine 10 mg daily, Zinc tablets twice daily and Inerson[®] zalf twice daily.

Discussion

Hepatitis C is an inflammation of the liver caused by HCV infection. The disease transmission is from direct contact with contaminated blood. This inflammation occurs in most of the infected people, but it depends on the intensity and duration. Unlike other hepatitis viruses, HCV does not induce adequate immune response so the acute manifestations are often subtle and most of the infected people become carrier of chronic hepatitis with long term consequences. The disease is also reported transmitted via secrete (breast milk, saliva, urine, and sperm). This virus can survive in the outside for 16 hours to 4 days. There are several genotypes (variant) of this virus. We order to establish the diagnosis of hepatitis C we need to identify the anti-HCV antibody using ELISA [2].

Autoimmune manifestations in chronic HCV infection is related to the epitopes cross reactions detected in viral and human polypeptide. For example, the presence of the same homolog sequence in cytochrome P4502E1 and protein HCV-NS5b is responsible for autoantibody production which targeted our own protein product. Other case of molecular similarity is the homolog of NS5 region and 3 human proteins, which are nitrogen oxide synthase, tyrosin kinase-Lck, proto-oncogen and liver growth factor activator. Thus, epitopes similarity between HCV and human autoantigen triggers autoantibody non-specific production, which causes tissue destruction and produce inflammatory reaction [15].

Dermatologic manifestations related to VHC infection are caused by three different viral actions. The direct action occurs in keratinocytes, lymphocytes, antigen presenting cells, dendritic cells, and blood vessels. The indirect action is related to immune complex development or autoimmune process. The third viral action is caused by the organic functional disturbance, which includes the dermatologic manifestations caused by organs that are not directly related to HCV viral infection [2].

Necrolytic acral erythema (NAE) is related to the necrolytic erythema group and metabolic syndrome. The clinical manifestation of NAE is shown as erythematous-violaceous plaques with well-demarcated border, hyperpigmentation, with scales, hyperkeratosis, and lichenification. These findings are often associated with itch or burning feeling. Necrolytic acral erythema may occur in patients who are 11-60 years of age, but the highest incidence occur in people of 35-55 years of age, and gender does not differ the incidence of NAE. Necrolytic acral erythema is often found in the dorsal part of feet, around Achilles tendon, and the knee [8]. Hepatitis C viral infection is considered pathognomonic for NAE. Skin findings may vary, depend on the stage of the lesion. Acute lesions show vesicles and flaccid bullae around the plaques. Chronic lesions show erythematous-violaceous plaques with thin scale, erosion, crusts, and usually dark red-colored. From the histopathology examination of the punch biopsy specimen we can find psoriasisiform hyperplasia with prominent confluence parakeratosis, hypergranulosis, and suprapapillary plates depletion. In the parakeratosis layer we can find a lot of neutrophils with neutrophilic microabscess. Hair follicle infundibular plugging with parakeratosis and neutrophils. Small vessels dilatation in dermal papilla and superficial perivascular lymphocytic and neutrophilic infiltration in dermis [9].

Based on a longitudinal observation, the evolution of NAE can be categorized into 3 stages. In the early stage, skin changes consist of erythematous papules which are 2-3 mm in diameter. Growth and the thickening of the papules extend and also accompanied by scales. Hyperpigmented papules or plaques is the early sign of erosion. Thus, the primary lesion is the papules or the erythematous-violaceous plaques with erythematous macules around it. In the development stage, the diameter and the thickness of the papules continue to grow, so does the scales and lichenification. Then, the erythema is replaced by hyperpigmentation and the scale production reduces. Necrosis of superficial epidermis is showed by the production of hyperpigmented crust. Pustules may develop, but not very often. In this stage, the border and the distribution of the lesion is the pathognomonic, so that we can establish the diagnosis of NAE. The plaques may persist for several months and may cause itchy feeling. In the late stage, the lesion become thinner and hyperpigmentation is prominent. The crust and erosion may persist in some cases. The distribution and well-demarcated border is more prominent in chronic lesion. The remission and exacerbation of this disease may happen spontaneously [16]. Several cases are successfully treated with 3 million units of subcutaneous interferon alpha, with zinc sulfate and amino acids orally [12].

In this case, the original lesions are flaccid bullae and erythematous plaques which then, developed hyperpigmentation, crusts, scales and lichenification. Skin scraping examination with 10% KOH solution shows negative result. The histopathological examination revealed psoriasisiform, hyperkeratosis, neutrophilic microabscess, epidermal necrosis, spongiosis, and epidermal inflammatory cells infiltrations. From the serologic anti-HCV obtained reactivity and increased level of AST/ALT.

The differential diagnoses of this case is necrolytic migratory erythema (NME), psoriasis, and corporal tinea. Necrolytic migratory erythema (NME) is pathognomonic for pancreas glucagonoma and more than two third of the patients are diagnosed with tumor. If NME occurs without underlying characteristic pancreas malignancy, this condition is called pseudoglucagonoma syndrome. Glucagonoma

is rare and only 400 cases have been recorded in literatures. There is no gender differences in glucagonoma incidence and the highest glucagonoma incidence occur in the sixth decades of life. The clinical manifestations of glucagonoma are commonly related to excessive glucagon. The amino acid level decreases due to glucagon stimulation to consume amino acid substrate for gluconeogenesis and to increase amino acid oxidation. The decreasing of amino acid (histidine and triptophane) induces pain, erythema, and intertriginosa erosion. Glucagon also increases skin arachidonat acid level, which also increases inflammatory mediators (prostaglandine and leukotrien), The skin lesion of NME is polymorphic, but erosion and crusts often occur. Erythematous plaques are the primary lesion of NME. It can develop into bullae and progressive erosion may occur. Itch and pain may also be complained by the patient. The predilection location is the intertriginosa area (inguinal, perineum, buttock, and lower abdomen), the center part of the face (perioral), and distal extremities. If the lesion extend to the mucosa, chielitis angular, glossitis atrophic, and stomatitis may occur. Histopathological of NME lesion, we can find upper epidermal necrosis from the spinosum layer and neutrophilia in acute lesions. In chronic lesion, dermatitis psoriasisiform, parakeratosis, and hyperkeratosis can be found in our patient, we did not find either mucosal lesion or pancreas glucagonoma, thus the diagnosis of NME can be excluded [17].

The other differential diagnosis is psoriasis. Psoriasis is a chronic papulosquamosa inflammatory disease with the characteristic of multiple remission and relapse [18]. The most common lesion of psoriasis is well-demarcated erythematous plaques with thick scales, but rarely sterile pustules can be found. The most common predilections of psoriasis are the scalp, the elbows, knees, nails, legs, and the trunk (including intergluteal fold). From the histopathological examination revealed acanthosis with elongated rete ridges, hypogranulosis, hyper and parakeratosis, dilated vessels, and lymphocytes and neutrophils perivascular infiltrate in the epidermis. Psoriasis can be found in people of all ages. External factors (Koebner phenomenon) and systemic factors (infection, HIV, endocrine, psychogenic stress, drugs, alcohol consumption, smoking, and obesity) may trigger the exacerbation of psoriasis [19]. In our patient, we found thin scales on the superior and inferior extremities but we did not find Koebner phenomenon as one of the triggering factors, so that the diagnosis of psoriasis can be excluded.

Other differential diagnosis is tinea corporis. Tinea corporis is a kind of dermatophytosis that occur in glabrous skin, except the palmar, plantar, and the inguinal. Tinea corporis is transmitted directly from the infected human or animal via fomites, or it can arise from autoinoculation of dermatophytes reservoir colonies of the feet. Children are more prone to zoophilic pathogens, especially *Microsporum canis* which is carried by dogs and cats. Occlusive clothes and damp climate increase the progression of the disease. Wearing occlusive clothes, skin to skin contact, and mild trauma may cause development of dermatophytes. Tinea corporis gladiatorum is often caused by *Trichopyton tonsurans*. The main predilection areas are the head, neck, and upper arm. The most common etiology of tinea corporis is *Trichophyton rubrum*. The clinical manifestations of tinea corporis are annular plaques (ringworm-like) or serpiginosa with scales on the active edges of the lesion, hyphae is also seen in KOH 10% examination [20, 21].

In our patient hyphae was not obtained in KOH 10% examination, therefore we ruled out diagnosis of tinea corporis can be excluded.

APPENDIX



Figure: (A) The facial region is normal (B-E) The upper and lower extremities with macules and multiple, discrete hyper/hypopigmented patches.

Conclusion

A case of a 59 years old woman, who complained about itchy erythematous-violaceous plaques on her arms and legs since 1 year ago has been reported. The patient has experienced this complain since she was infected with hepatitis C virus 2 years ago. From the physical examination we found multiple well-demarcated erythematous-violaceous plaques on the superior and inferior extremities with hyperpigmentation, discrete, and accompanied by thin scales and lichenification. The histopathological examination using HE staining we found psoriasiform image, hyperkeratosis, neutrophilic microabscess, epidermal necrosis, spongiosis, and inflammatory cells infiltration in the epidermis. The HCV infection is patognomonic for NAE. The skin lesion of this patient is continue to improve simultaneously with the hepatitis C disease she suffers from.

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