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Case Report

TORCH re-activation concomitant with drug-induced hypersensitivity syndrome shows erythema multiforme-like and vasculitis clinical features

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Abstract

Background: Drug-induced hypersensitivity syndrome (DIHS) can be associated with cytomegalovirus (CMV) infection, besides induced by drugs. We report a case of DIHS with prolonged atypical clinical features and vasculitis precipitated by drug allergy, CMV, and other viral infections.
Case illustration: A 54-year-old female presented with generalized follicular erythematous papules and waxy palmoplantar keratoderma since one month before admission. The symptoms started as a purpuric lesion on the upper extremities, spreading as erythematous papules on the trunk with facial edema, accompanied by fever and chronic cough. She had been previously treated with ambroxol and cephalosporin. Cutaneous drug allergy reaction was assessed. Although in therapy with systemic corticosteroids, lesions still appeared and became confluent, with new palpable purpura on the extremities. Histopathology showed interface dermatitis, consisting of lymphocytes and plasma cells but lacking eosinophils, leukocytoclastic vasculitis, and numerous dyskeratotic keratinocytes. The possibility of systemic infection was sought, and TORCH examination suggested acute and latent infection. The patient had a positive PCR for CMV. Intravenous ganciclovir 500 mg/day for three weeks and a low dose of systemic corticosteroids led to complete cessation of skin and pulmonary symptoms.
Discussion: The clinical and histopathological examination was consistent with erythema multiforme. Therefore, high titer of IgM and IgG anti-CMV, and excellent response to ganciclovir supported our suspicion of an infection-induced process. The infection might be precipitated by a drug allergy.
Conclusion: CMV-associated skin lesion could be precipitated by drug hypersensitivity, resulting in erythema multiforme-like clinical features with vasculitis. Severe systemic involvement related to CMV reactivation. Early anti-CMV therapy showed good improvement and reduce risk of mortality.

Keywords: *cytomegalovirus, drug hypersensitivity, DIHS, vasculitis*

Background

Drug hypersensitivity remains an important clinical issue. It consists of various phenotypes, mainly cutaneous adverse reactions ranging from milder skin reactions to severe cutaneous adverse reactions (SCARs). SCARs are life-threatening, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS).[1]

DIHS is associated with the reactivation of herpes viruses, especially human herpesvirus 6 (HHV-6) and cytomegalovirus (CMV). DIHS tends to have a relatively later onset than other types of drug eruptions, approximately 2–8 weeks after the administration of the causative drug. DIHS is

usually associated with only a limited number of drugs, including carbamazepine, phenytoin, phenobarbital, lamotrigine, dapsone, mexiletine, salazosulfapyridine, allopurinol, and minocycline.[1]

Cytomegalovirus (CMV), a member of the Herpesviridae family, is an opportunistic infection with a typically benign course in the immunocompetent person but could have a severe course in the immunocompromised one. CMV infection usually affects visceral organs, mostly the respiratory and gastrointestinal tract. Cutaneous manifestations caused by CMV are rarely reported and have various forms, such as morbilliform rash, petechiae, purpura, and vasculitis.[2,3] Vasculitis associated with CMV seems to be a more fulminant disease with fatal outcomes in the majority of cases.[2-4] Here, we present a case of DIHS triggered by cytomegalovirus coexisting with other viral infections (TORCH) with atypical features of targetoid lesions, vasculitis, and ulceration.

The prognosis of DIHS/DRESS is highly variable and unpredictable either short-term or long-term. The cause of mortality in DIHS/DRESS have been described in previous studies mainly due to complications such as myocarditis, *Pneumocystis jirovecii* pneumonia, gastrointestinal bleeding and sepsis.[5]

Case Illustration

A 54-year-old female came to the outpatient clinic with a chief complaint of erythematous itchy patches on the face, neck, trunk, hand, and red dots on her extremities in the last 4 weeks before admission (figure 1). The lesions began with a single red dot on her right arm and had a generalized spreading in several days. She also complained of fever and chronic sign of respiratory infection, previously treated with cephalosporin, paracetamol, and ambroxol ten day before the lesion appeared. She was diagnosed with drug eruption in a previous hospital and treated with intravenous steroids with no significant improvement. The erythematous plaques and petechial lesions worsened. No history of contact irritant or allergen.

On physical examination, we found facial edema and fever 39^{o}C with multiple and confluent erythematous plaques on the upper and lower part of the body, with vasculitis lesions on both legs. There were several atypical/targetoid lesions on her legs (figure 2) and hyperkeratosis of palmoplantar (figure 4). We also found multiple ulcerations in the perianal region with a kissing-like appearance (figure 3).

Laboratory abnormalities include leukocytosis with eosinophilia (2.6 x 109/L) and elevation of blood urea and creatinine level three times more than normal, supporting drug-induced hypersensitivity syndrome (DIHS). She also had elevated blood glucose, electrolyte imbalance, and high lactate dehydrogenase level. Other differential diagnoses at that time were erythema multiforme, secondary syphilis, and Rowell syndrome. The patient underwent skin biopsy and other laboratory examinations to exclude other differential diagnoses.

Histopathology from the erythematous plaque on the abdominal area and purpuric papules on the lower leg showed orthokeratosis with focal parakeratosis, scattered necrotic keratinocytes, and heavy infiltrate consisting of lymphocytes, plasma cells, but lacking eosinophils in the dermo-epidermal junction (interface dermatitis). There was also vascular damage with neutrophil infiltration, nuclear dust, and extravasated erythrocytes (figure 5).

There was no reactivity on the syphilis serological test. ANA was positive with titer 1/100, and C3 and C4 complement levels were normal. There was reactivity of anti-toxoplasma IgM, with a cut-off index (COI) of 1, anti-rubella IgG (162.3 IU/mL), anti-CMV IgM (COI 6.5), anti-CMV IgG (2242 U/mL), anti-HSV 1 IgM (COI 3.45), anti-HSV 1 IgG (COI 2.41), anti-HSV 2 IgM (COI 1.44), and anti-HSV 2 IgG (COI 1.33). HBsAg and anti-HCV tests were negative. HIV test results were negative, but CD4+ and CD3+ cell counts were low (175 and 442 cells/µL, respectively).

The diagnosis of DIHS was sought, following a 6-score with the scoring system for RegiSCAR (definite for DIHS), which consisted of the need for hospitalization, reaction suspected to be drug-related, acute skin rash, fever, eosinophilia, and renal involvement. We administered 1 mg/BW oral corticosteroid, but there was no significant improvement after seven days of administration. Meanwhile, within several days of admission, the erythematous plaques began to spread all over the body with some areas of normal skin. Petechiae and purpuras slowly transformed into erythematous plaques.

Clinicopathology and laboratory findings led us to the diagnosis of vasculitis caused by drug allergy coexisting with other virus infections. Drugs previously consumed by the patient could precipitate skin abnormalities. The targetoid lesions on the legs, kissing-like ulcers in the genital, and the HSV-1 and HSV-2 antibody

reactivity also supported the diagnosis of erythema multiforme and genital herpes.

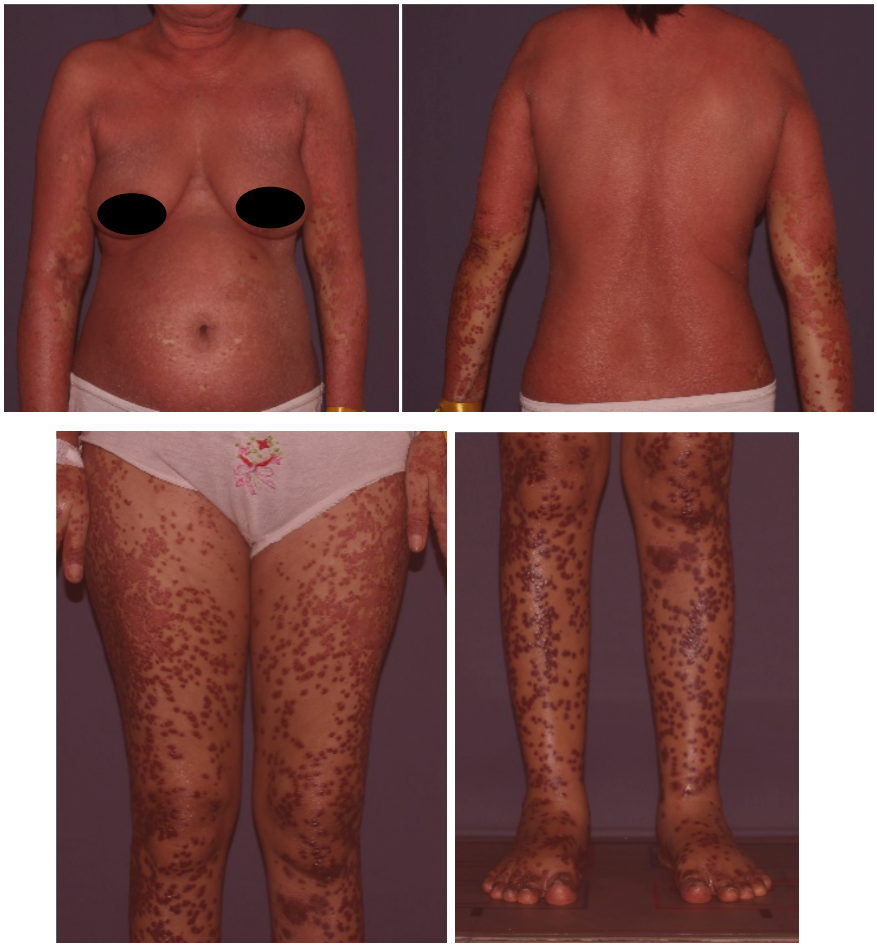

Figure 1. Erythematous plaques on the upper and lower part of the body, with vasculitis lesions on both legs

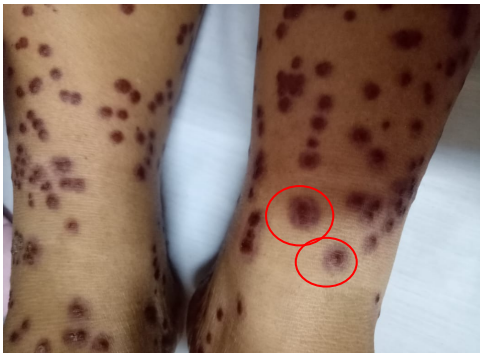

Figure 2. Target-like/atypic lesions on lower legs (red circle)

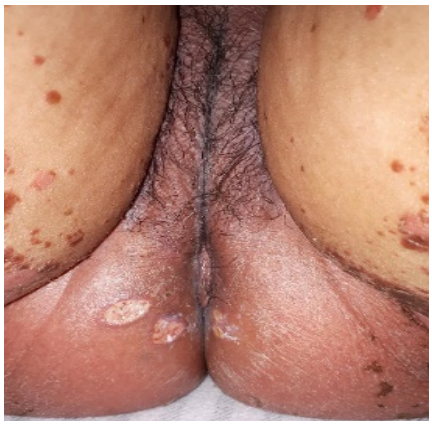

Figure 3. Multiple perianal ulcers

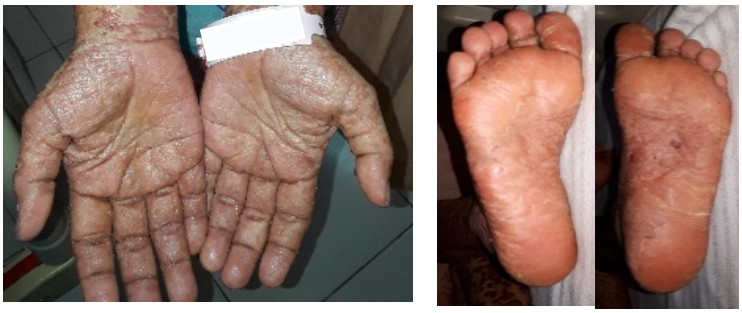

Figure 4. Hyperkeratosis of palmoplantar

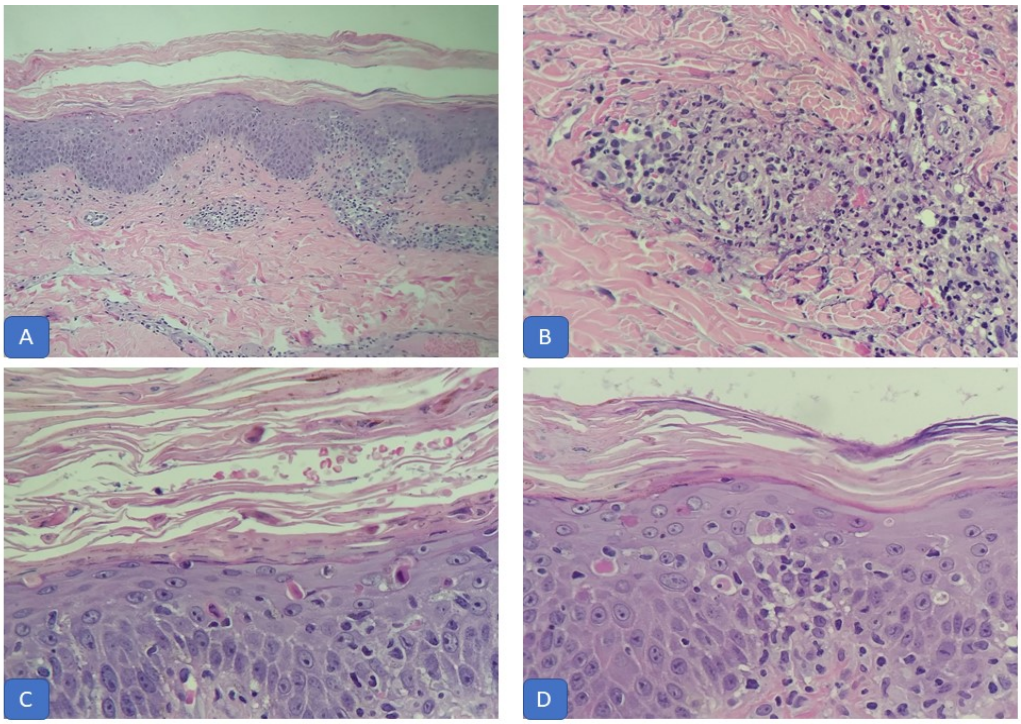

Figure 5. Histopathology interpretation **A.** Hematoxylin-eosin (HE) 100X. Orthokeratosis with focal parakeratosis; scattered necrotic keratinocytes and heavy lymphocytic infiltrate in the dermo-epidermal junction (interface dermatitis) **B.** HE 400X. Vascular damage, with neutrophil infiltration, nuclear dust and extravasated erythrocytes **C-D.** (HE, 400X). Exocytosis of lymphocytes and extravasated erythrocytes

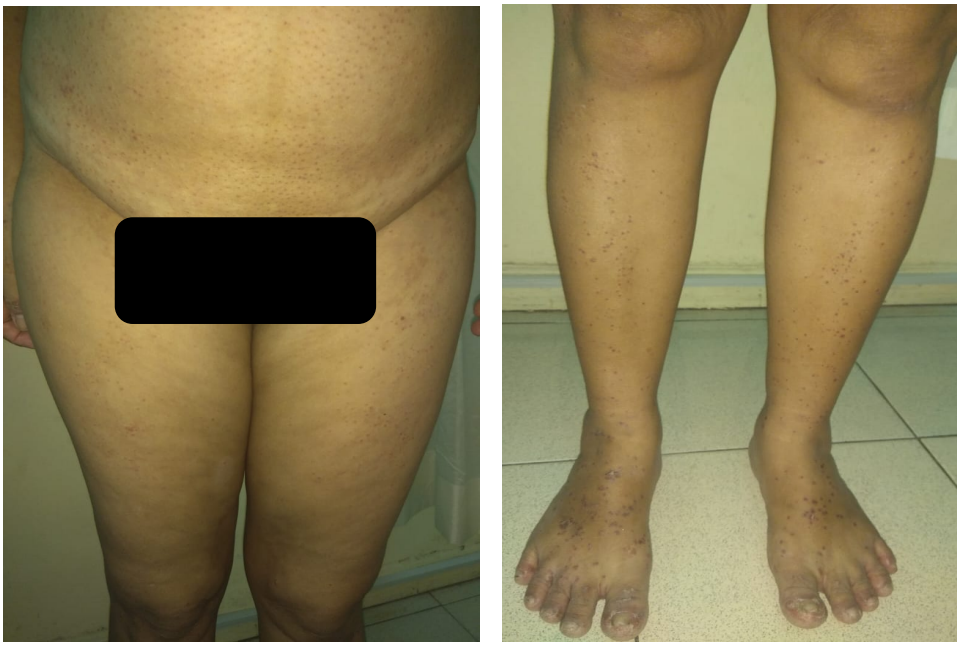

Figure 6. Three months after treatment; multiple hyperpigmentation macules, discrete

The patient also had a cough and dyspnea for several days before admission. Chest X-rays showed diffuse infiltrate on bilateral lower lungs, suggesting interstitial lung disease hypersensitivity pneumonitis. Thorax CT scan revealed no specific features for CMV pneumonitis. She was first diagnosed with community-acquired pneumonia by the respirology division. Three weeks after admission, the cough and dyspnea worsened, and she experienced acute respiratory distress syndrome. Further evaluation of the pulmonary condition led to the diagnosis of CMV pneumonitis.

We started administering ganciclovir 500 mg/day for 21 days. Oral corticosteroid was also continued alongside antiviral administration. No new lesion appeared and improvements in skin lesions were seen within the first week, and the pulmonary symptoms also improved in 3 weeks after antiviral administration. Three months after treatment; skin lesion resolve to multiple hyperpigmentation macules, discrete (Figure 6)

Discussion

Cutaneous cytomegalovirus is rarely reported due to difficulty in identifying the clinical and pathological features. The most common dermatologic manifestations of CMV are perianal and oral ulcers, but many other dermatological manifestations can complicate the diagnosis. A review by Drozd, et al.[2] mentioned that cutaneous CMV could manifest as morbilliform rash, petechiae, purpura, plaques, vesicles, bullae, erosions, erythema, nodules, papules, edema, vasculitis, and pustules. In this review, four patients were diagnosed with CMV reactivation after drug-induced hypersensitivity syndrome (DIHS), resulting in cutaneous manifestations that resolved only when the CMV infection was treated. The complete mechanism has not been elucidated, but there is evidence of the reactivation of latent CMV by DIHS.[6] The clinical presentation ranges from ulcerated erythematous plaques and papules to widespread, dark-erythema, and purpura. It has been proposed that the drug in DIHS causes expansion of the regulatory T-cell population, which reactivates latent herpes viruses. Tissue damage occurs due to activated CD8+ T-cells that target viral antigens.[2-3]

Petechiae is a rare cutaneous manifestation of CMV, as seen in our patient. Cases of CMV-related petechiae were initially diagnosed as secondary immune thrombocytopenic purpura (ITP) or microangiopathy-related CMV, which were diagnosed after refractory treatment for primary ITP.[2] In this patient, skin lesions started as petechiae, which then transformed into erythematous papules and plaques, typical for vasculitis lesions.

The appearance of erythematous plaques with palmoplantar keratoderma in our patient is questionable because it does not fit DIHS and the rapid onset of lesions following two days of

exposure to offending drugs. Petechiae, as the first emerging lesion preceding almost all of the lesions, was distinctive. The severity of lesions also increased with the consumption of certain drugs, indicating that drug hypersensitivity induced the latent virus to reactivate. Interestingly, not only CMV infection manifested by vasculitis appears, but also the presence of erythema multiforme-like lesions and perianal ulcers. The characteristic lesion of erythema multiforme in the form of a target lesion with 3 ring zones was not found in the patient.

The reactivity of CMV, HSV-1 and 2, toxoplasma, and rubella antibodies could also raise suspicion of multiple viral reactivations by drug allergy. Reactivation of CMV has been implicated in driving DIHS through viral T-cell expansion and drug-antigen cross-reactivity.[7] In an analysis of peripheral blood T cells (CD4 and CD8) in 40 patients with DIHS due to allopurinol, sulfonamides, and carbamazepine, over 70% of patients demonstrated EBV, HHV6, or HHV7 reactivation. The activation of CD8 was present in all patients in the skin, liver, and lungs, and tumor necrosis factor-α and interferon-γ levels correlated with the severity of systemic involvement. Drug-related viral reactivation and the ensuing immune response to viral epitopes explain how multi-organ symptoms occur long after discontinuation the culprit drug.[8] The mortality of DIHS approximately 10% and often related to unrecognized myocarditis and cytomegalovirus complications, with longer-term consequences that contribute to morbidity.[9]

The histopathological results revealed patterns corresponding with interface dermatitis, as usually seen in erythema multiforme. This was the starting point that we looked for the probability of infection as the triggering factor in our patient. This suspicion was also supported by the fact that cessation of a certain drug (i.e.insulin) followed by systemic corticosteroids failed to give satisfactory results. Thus, leucocytoclastic vasculitis was thought to result from the same process, with a viral infection as a possibility.

The histological features that could lead to CMV-skin infection are intranuclear inclusions surrounded by a clear halo (owl's eye inclusions), dermal vessel dilatation, and prominent perivascular neutrophilic infiltration. Signs of infection were not observed in the epidermis or in the eccrine structures as previously reported.[3]
Our patient's low CD4+ cell counts indicated an immunocompromised condition, although the HIV test results were negative. This immunocompromised condition could lead to the appearance of all TORCH infections. Treatment of CMV is often simple, yet making the correct diagnosis often needs prolonged time and complicates the management. Early detection is important to prevent mortality, especially in the immunocompromised. In our patient, although it was slow, skin lesions were improved after administration of ganciclovir, supporting the diagnosis of cutaneous-related CMV infection. Previous studies indicated that CMV reactivation are the cause of fatal complications occurring in the late stage of DIHS, could be preventable with anti-CMV therapy. In support of this possibility, a delay in initiating anti-CMV therapy after the first detection of CMV reactivation was likely to reduce efficacy.[10]

Conclusion

As seen in our patient, CMV-associated skin lesion could be precipitated by drug hypersensitivity syndrome, resulting in a prolonged atypical vasculitis. TORCH examination seems to be a useful screening test for such infection. Excellent response with ganciclovir and oral corticosteroid administration indicated that the cytomegalovirus infection precipitated by drug allergy was the nature of this disease.

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