

of oncological patients. Therefore, the identification of patients with lower HI and early use of moisturizers and emollient creams could help prevent clinical symptoms. Collaborative studies, with larger sample sizes, on the role of HI in the evaluation of skin tolerability for targeted therapies are ongoing. ■

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IgA nephropathy preceded by erythroderma with eosinophilia

A 60-year-old male was referred to us with a one-year history of erythroderma on his whole body. His skin lesions had been refractory to topical treatment. His medical history was unremarkable, except for hypertension and hyperlipidaemia. His family had no health problems. Examination revealed flat erythematous lesions scattered on the whole body, often coalesced into plaques (*figure 1A, B*). The eruptions were very itchy. Skin biopsy specimens showed mild spongiosis in the epidermis, with a focal vacuolar change in basal keratinocytes (*figure 1C*). There was no atypical lymphocyte infiltration in the skin specimens. Direct immunofluorescence showed no deposition of immunoglobulins or complements in the skin. Laboratory examination revealed severe eosinophilia: white blood cells at 11.6×10^9 cells/L (reference range: $4.0\text{--}10 \times 10^9$ cells/L), with 29.0% eosinophils (reference range: 0.4–8%). Hepatic function and renal function were within normal limits. Neither anti-nuclear antibodies nor anti-HTLV1 antibodies were detected.

The cessation of medications, which included anti-hypertensive drugs, did not improve his symptoms. Whole-body computed tomography revealed multiple lymphadenopathies in the inguinal area. However, lymph node biopsy specimens showed no malignancies. Bone marrow aspiration did not reveal any atypical blood cells. Flow cytometric analyses of the bone marrow revealed CD3⁺ (75.4%), CD4⁺ (36.4%), CD8⁺ (41.2%), and CD2⁺ cells (82.3%). FIPIL1-PDGFRa fusion, a hallmark of chronic eosinophilic leukaemia, was not detected. During physical and laboratory examinations, his renal function gradually deteriorated, prompting a renal biopsy. The kidney specimens showed sclerotic changes in the glomeruli. Immunofluorescence revealed IgA deposition in the mesangial area (*figure 1D*). The diagnosis of IgA nephropathy was made. The patient underwent pulsed corticosteroid therapy, which resulted in the complete remission of the renal dysfunction, skin symptoms, and eosinophilia. The corticosteroids were gradually reduced to 4 mg prednisolone/day. No obvious recurrence of nephropathy, erythroderma, or eosinophilia was observed at five years.

Erythroderma is a skin condition characterized by diffuse erythema and scaling of the skin all over the body ($\geq 90\%$ based on the most common definition) [1]. Differential diagnoses of erythroderma include psoriasis, lichen planus, eczema, ichthyosis, mycosis fungoides and Sézary syndrome. Underlying diseases, such as graft-versus-host disease, diabetes mellitus and internal malignancy, are also known causes [1]. To the best of our knowledge, IgA nephropathy has not been associated with erythroderma in

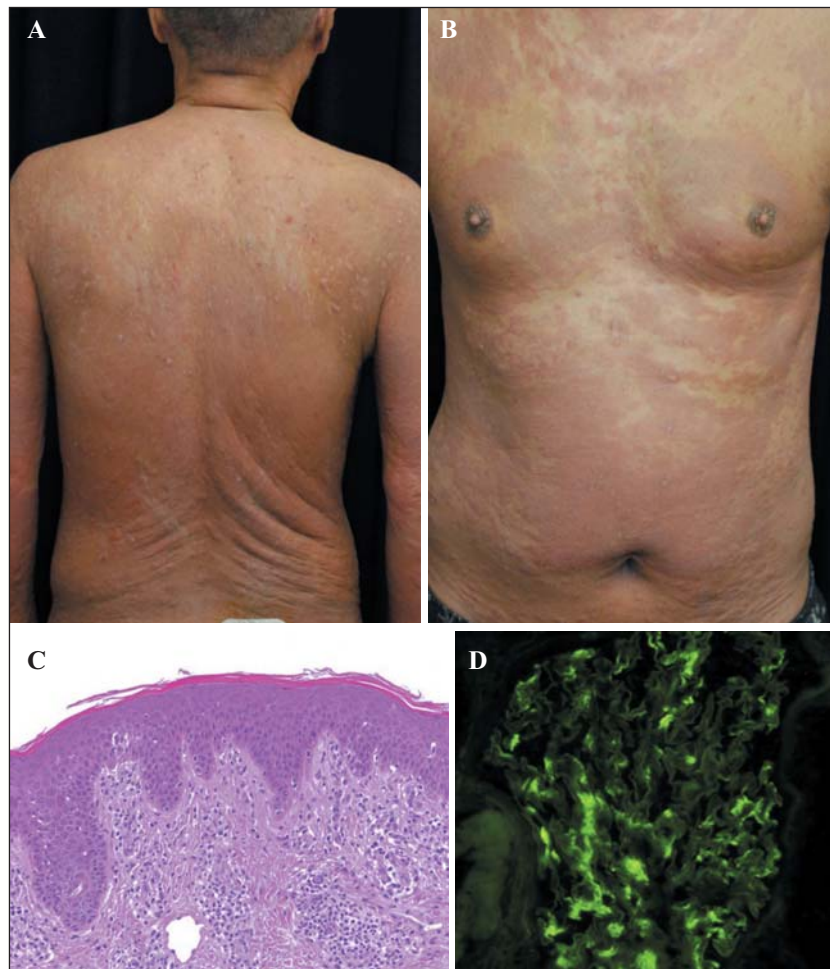


Figure 1. A, B) Clinical manifestations showing extensive erythema on the back (A) and the abdomen (B). C) Skin biopsy specimen (haematoxylin and eosin staining; original magnification: x200). D) Immunofluorescence of the renal biopsy specimen reveals IgA deposits in the glomerular mesangium (original magnification: x400).

the literature, except a case with extensive psoriasis with IgA nephropathy [2]. In our case, the diagnosis of psoriasis was excluded by skin histopathology. We suspected that the patient had erythroderma secondary to eczema, but this scenario was unlikely because his eruptions did not respond to topical corticosteroids. Therefore, the erythroderma in our case might have stemmed from peripheral blood eosinophilia.

Peripheral blood eosinophilia is also a risk factor for end-stage kidney disease (classified by $\text{eGFR} \leq 5 \text{ mL/min/1.73m}^2$) based on multiple aetiologies, including IgA nephropathy [3]. Our case points to the necessity of a check-up of the kidneys when unexplained eosinophilia is seen. The most common eosinophilic disease associated with IgA nephropathy is Kimura's disease, which is recurrent cervical lymphadenitis. Our case showed no such lymph node inflammation in the head or neck. Furthermore, hypereosinophilic syndrome (HES) [4] was excluded in our case because dense eosinophil infiltration was not observed in the skin, lymph nodes, or kidneys. Eosinophilic infiltration is not always present in the kidney specimens of eosinophilia-induced renal diseases [5]. Therefore, it is most likely that the renal dysfunction in our case resulted from an inflammatory response indirectly induced

by eosinophils through the secretion of cytokines (*e.g.*, $\text{TGF-}\alpha$, $\text{TGF-}\beta$, $\text{TNF-}\alpha$, IL-6, and IL-8) [5].

The lymphocytic variant of hypereosinophilic syndrome (L-HES) is an HES subtype driven by cytokines produced by $\text{CD3}^+ \text{CD4}^+$ T-cells and can accompany erythroderma [6]. L-HES was a differential diagnosis in our case, but as our routine testing did not include multi-colour labelling, we were unable to confirm $\text{CD3}^+ \text{CD4}^+$ populations. In any case, the proportion of CD3^+ and CD4^+ cells was not skewed in the bone marrow. Accordingly, the peripheral blood eosinophilia in our case might be categorized as idiopathic.

In summary, this is the first reported case of IgA nephropathy preceded by erythroderma with eosinophilia. When primary skin diseases and underlying malignancies are ruled out as the cause of erythroderma with eosinophilia, clinicians must look into the dysfunction of other organs, including the kidneys. ■

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Exacerbation of livedoid vasculopathy after coronavirus disease 2019

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 typically presents with fever, fatigue, myalgia, headache, diarrhoea, cough and dyspnoea [1], and was declared a pandemic by the World Health Organization on 11th March, 2020. Cutaneous manifestation of COVID-19 was first described as a “rash” and was observed in 0.2% of 1,099 hospitalized patients in China [2]. The reason why there were so few reports of cutaneous symptoms may be because cutaneous lesions were not generally included in the COVID-19 clinical spectrum. Recalcatti was the first to analyse cutaneous manifestations that were identified in about 20% of COVID-19 patients [3]. Despite the increasing incidence of cutaneous manifestations of SARS-CoV-2 infection, effects of COVID-19 on patients with underlying cutaneous diseases are rarely reported. Here, we describe the exacerbation of livedoid vasculopathy (LV) by SARS-CoV-2 infection.

A 68-year-old man visited our clinic due to worsening lower leg pain after three days of asymptomatic SARS-CoV-2 infection. In 2009, he was diagnosed with LV after physical examination and histopathological analysis (figure 1A, B). He had been taking clopidogrel bisulphate for 10 years with no associated adverse effects.

Physical examination revealed bilateral brownish erythematous livedoid skin changes on the lower limbs and painful palpable erythema with crusting on the ankles. One month after the COVID-19 outbreak, he experienced skin ulceration. Treatment with rest and topical treatment improved the ulcer after three months (figure 1C).

The cutaneous manifestations of COVID-19 are classified into six main clinical patterns: (1) urticarial rash; (2) confluent erythematous/maculopapular/morbilliform rash; (3) papulovesicular exanthem; (4) chilblain-like acral pattern; (5) livedo reticularis/racemosa-like pattern; and (6) purpuric “vasculitic” pattern [4]. Although the exact pathophysiology of these symptoms is unknown, hyperactive immune response, complement activation, microvascular injury, vasculitis, vascular thrombosis and neoangiogenesis are implicated [4]. Pulmonary and cutaneous thrombotic microvascular damage with deposition of complement protein and SARS-CoV-2 spike glycoprotein were reported in five patients with COVID-19 and severe respiratory failure [5]. The complement component of SARS-CoV-2-specific spike glycoprotein was present in both the lungs and skin. COVID-19 may induce thrombotic microvascular injury syndrome via activation of alternative and lectin complement pathways [5], thereby resulting in cutaneous manifestations such as LV. Furthermore, high levels of von Willebrand factor (vWF) are common in COVID-19 patients, possibly due to endothelial damage. An explanation for this could be that SARS-CoV-2 enters cells via the transmembrane protein angiotensin-converting enzyme (ACE) 2 [6]. ACE2 is expressed on the surface of alveolar epithelial cells, as well as arterial and venous endothelial cells [7]. The entry of the virus could contribute to inflammation and damage of endothelial cells causing release of prothrombotic mediators, primarily vWF from Weibel–Palade storage bodies, and exposing underlying collagen to which vWF binds [6].

LV is a condition of thrombotic vasculopathy, which manifests as recurrent reticulated purpura of the legs associated with erythematous or purpuric papules. The reticulated purpura develops into small ulcers and eventually heals to form atrophie blanche [8]. Histopathologically, LV is thrombosis in the blood vessels of the dermal vascular endothelium [9, 10]. Inactivation of antithrombotic function in the dermal vascular endothelium is the most likely aetiology of LV. As previously described, livedo reticularis is a cutaneous manifestation of COVID-19. We speculate that the eruption was exacerbated by SARS-CoV-2 infection due to the overlap in aetiology.

We describe the first case of LV exacerbated by SARS-CoV-2 infection. COVID-19 can induce peripheral vasoconstriction in patients with LV, resulting in vasoocclusive lesions and skin ulcers. This study highlights the importance of considering the possibility of LV exacerbation in patients with COVID-19, even in asymptomatic cases. ■

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