

World Journal of *Clinical Cases*

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ABOUT COVER

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The primary aim of *World Journal of Clinical Cases* (WJCC, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

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Successful treatment of lichen amyloidosis coexisting with atopic dermatitis by dupilumab: Four case reports

Qing Zhu, Bing-Quan Gao, Jin-Fang Zhang, Li-Ping Shi, Guo-Qiang Zhang

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Abstract

BACKGROUND

Lichen amyloidosis (LA) is a chronic, severely pruritic skin disease, which is the most common form of primary cutaneous amyloidosis. The treatment of LA has been considered to be difficult. LA may be associated with atopic dermatitis (AD), and in this setting, the treatment options may be more limited. Herein, we report four cases of LA associated with AD successfully treated by dupilumab.

CASE SUMMARY

In this article, we describe four cases of patients who presented with recurrent skin rash accompanied by severe generalized intractable pruritus, diagnosed with refractory LA coexisting with chronic AD. Previous treatments had not produced any apparent improvement. Thus, we administered dupilumab injection subcutaneously at a dose of 600 mg for the first time and 300 mg every 2 wk thereafter. Their lesions all markedly improved.

CONCLUSION

Dupilumab may be a new useful treatment for LA coexisting with AD.

Key Words: Lichen amyloidosis; Atopic dermatitis; Dupilumab; Biologics; Interleukin-31; Case report

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Core Tip: Lichen amyloidosis (LA) is a chronic, severely pruritic skin disease, which is the most common subtype of primary cutaneous amyloidosis characterized by deposition of amyloid protein on the skin without visceral involvement. The treatment of LA has been considered difficult, with high relapse rates. In this article, we present four cases of LA associated with atopic dermatitis (AD) treated with dupilumab who achieved remarkable results. Our observations suggested that dupilumab may shed light on the systematic treatment of refractory LA patients with AD.

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INTRODUCTION

Lichen amyloidosis (LA) is the most common subtype of primary cutaneous amyloidosis (PCA) characterized by deposition of amyloid protein in the skin without visceral involvement. PCA is commonly observed in Southeast Asian countries and LA appears to be more prevalent in those of Chinese descent. LA typically presents as persistent hyperkeratotic skin-colored or hyperpigmented papules usually located on the calves and other extensor surfaces, *e.g.*, anterior thighs or forearms, which can then coalesce into corrugated patches that often have a rippled or ridged pattern accompanied by severe itching. At the onset, lesions are usually unilateral, but overtime a bilateral symmetric distribution can develop. Histologically, LA appears as eosinophilic amorphous deposits that are restricted to the upper dermis particularly the papillary dermis with epidermal acanthosis and orthohyperkeratosis. The treatment of LA has been considered difficult, with a high relapse rate. Generally, many medical and physical treatments such as laser and light therapies have been tried with unsatisfactory results. LA associated with atopic dermatitis (AD) has been reported previously. We present four cases of LA associated with AD treated with dupilumab that demonstrated remarkable therapeutic achievements (Table 1).

CASE PRESENTATION

Chief complaints

Case 1: The patient was a 37-year-old man who presented with recurrent skin rash accompanied by severe generalized intractable pruritus for more than 14 years.

Case 2: A 67-year-old man presented with recurrent rashes on his back and limbs, which was most consistent with the characteristics of the nummular variant of AD, with generalized and intense pruritus for 10 years.

Case 3: A 20-year-old man visited our department presenting with multiple pruritic brownish papules that were mostly located on the anterior chest, back, and both thighs for 6 years.

Case 4: A 54-year-old woman presented with skin lesions along with pruritus which appeared 3 years prior to current presentation.

History of present illness

Case 1: The patient had received treatment with a variety of oral antihistamines and topical hormone creams for external use, but without satisfactory result.

Case 2: Prior treatment consisting of halometasone ointment for external use, oral antihistamine, and narrow band ultraviolet B phototherapy showed no benefit, and the rash continued to be worsened.

Case 3: The patient had received treatment with oral epinastine and mometasone furoate for external use, but without obvious effects.

Case 4: The patient had a history of irregular consumption of oral methylprednisolone tablets and epinastine hydrochloride capsules, but without satisfactory effects.

History of past illness

Case 1: The patient had suffered allergic rhinitis for more than 14 years.

Table 1 Clinical features of the four cases

Cases	Age/gender	Duration	Absolute value of eosinophils at baseline	Duration of treatment for absolute value of eosinophils decreased to normal range	Total serum IgE at baseline	Duration of treatment for total IgE decreased to normal range	EASI at baseline	EASI at 16 wk of treatment	VAS at baseline	VAS at 16 wk of treatment	DLQI at baseline	DLQI at 16 wk of treatment
Case 1	37 yr/male	14 yr	$6.30 \times 10^9/L$	6 wk	277.30 IU/mL	10 wk	62	16	10	1	22	3
Case 2	67 yr/male	10 yr	$0.10 \times 10^9/L$	-	54.20 IU/mL	-	36	10	8	0	19	1
Case 3	20 yr/male	6 yr	$0.20 \times 10^9/L$	-	1002 IU/mL	12 wk	16	4	6	0	16	2
Case 4	54 yr/female	5 yr	$2.0 \times 10^9/L$	10 wk	893.60 IU/mL	14 wk	23	8	7	0	17	1

Range of the normal absolute value of eosinophils: $0.00-0.52 (\times 10^9/L)$; Total serum IgE: < 100 IU/mL. EASI: Eczema area and severity index (0-72 scores); VAS: The pruritus visual analog scale (0-10 scores) (with the zero indicating no pruritus and 10 indicates most severe pruritus); DLQI: Dermatology life quality index (0-30 scores).

Case 2: The patient had a past history of allergic rhinitis for 20 years.

Case 3: The patient had suffered allergic rhinitis for 1 year.

Case 4: No significant past history or any illness.

Physical examination

Case 1: A dense distribution of hard and solid confluent plaques and papules was seen throughout the body, covered with dry and thick scales (Figure 1A-D).

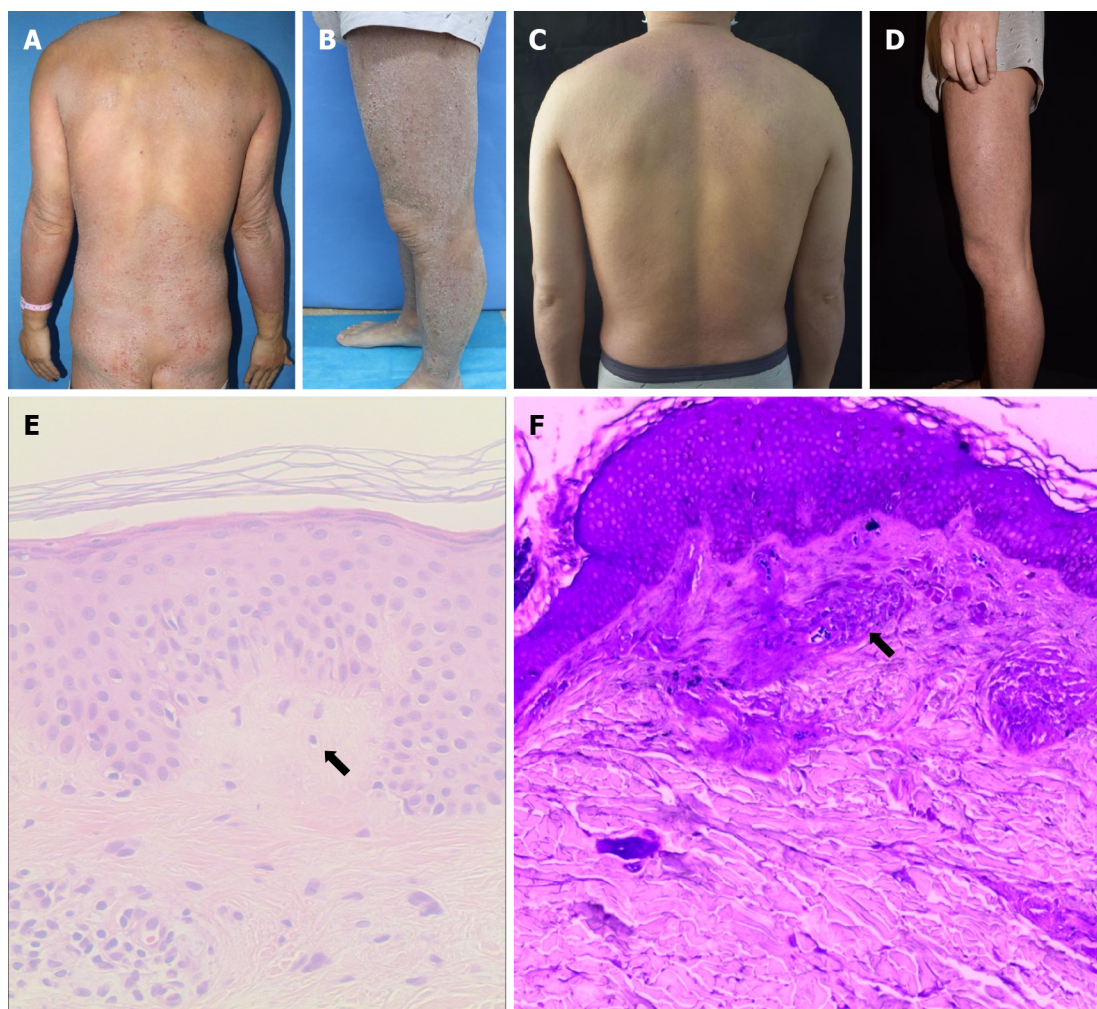
Case 2: Cutaneous examination revealed a dense distribution of hard and solid papules and irregular erythematous patches with unclear boundaries distributed in the back and limbs, which were covered with dry scales. Most of the skin was mossy and rough (Figure 2A-D).

Case 3: Upon dermatological examination, a dense distribution of solid and unmixing papules was seen on the back, anterior chest, and both thighs, which were covered with white scales. The skin showed lichenoid changes with a rippled pattern, which were more prominent on the lateral side (Figure 3A-D).

Case 4: A physical examination showed localized discrete brownish papules in association with erythema of different sizes on the neck, trunk, and lower limbs. Lichenoid skin changes and bloody crusts could be seen on the back and lateral aspects of shins. In addition, multiple firm and pigmented papules were symmetrically and densely distributed on the anterolateral surfaces of the calves (Figure 4A-D).

Laboratory examinations

Case 1: Laboratory examination demonstrated a total serum IgE level of 277.30 IU/mL and an absolute eosinophilic value of $6.30 \times 10^9/L$. The histopathological examination of the specimen obtained from the



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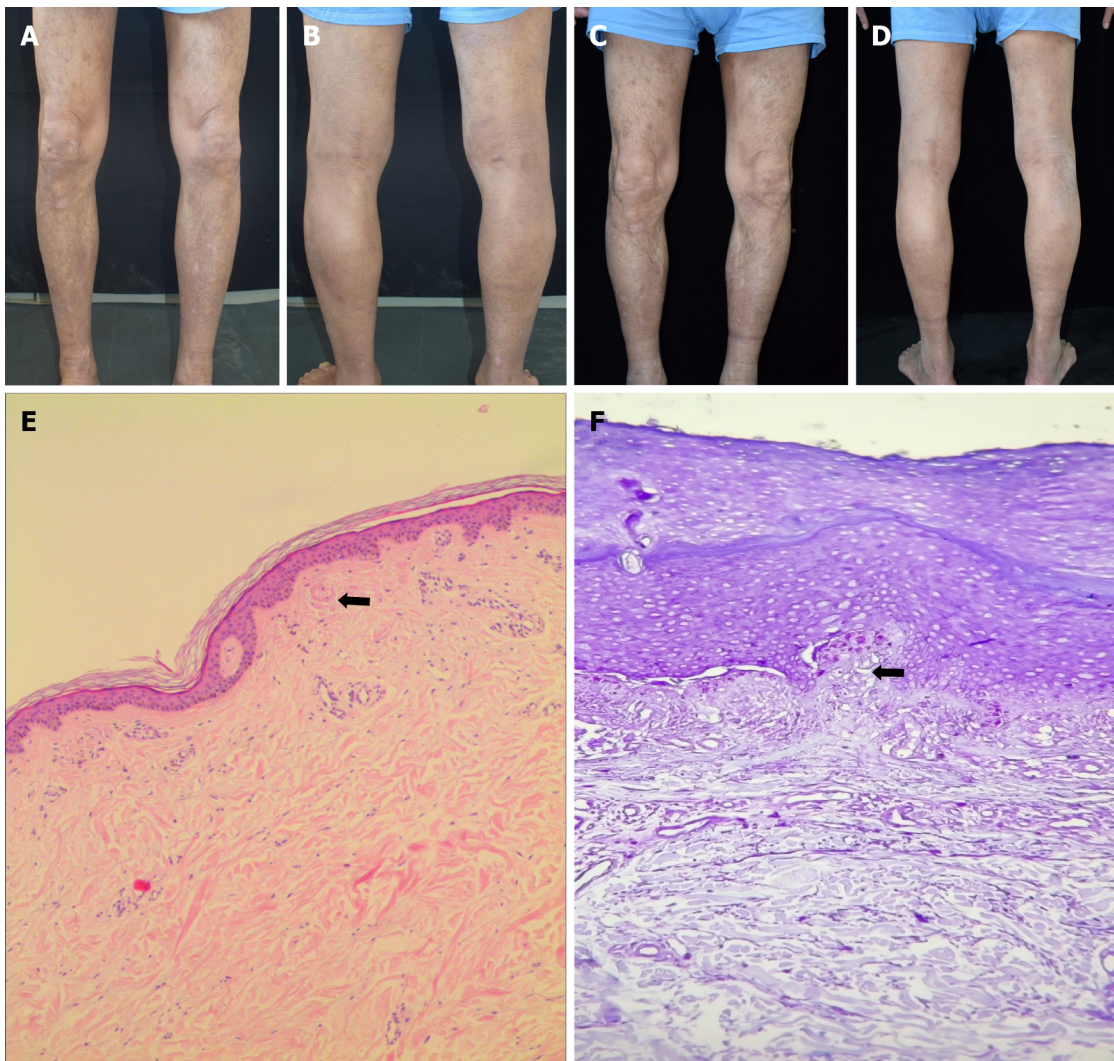
Figure 1 Case 1. A and B: Dense hard brown plaques were seen on the trunk and limbs at baseline; C and D: After 16 wk of treatment with dupilumab, the trunk rash basically subsided, the lower limb rash markedly improved, and the plaques became flat. The remaining lesions on the thigh after treatment, showed a characteristic rippled appearance indicating lichen amyloidosis as a co-existing condition; E: Histopathological examination revealed mild hyperkeratosis of the epidermis, irregular hyperplasia of the spinous layer, and spongy edema, with the dermal papilla and upper dermis showing a uniformly reddish mass that expanded the dermal papillae and displaced the rete ridges laterally (hematoxylin & eosin staining, $\times 100$); F: Crystal violet staining was positive for amyloid deposits in the dermal papillae and upper dermis with characteristic fissures (crystal violet staining, $\times 400$). The arrow indicates amyloid deposits.

back area showed mild hyperkeratosis of the epidermis, irregular hyperplasia of the spinous layer, spongy edema, complete basal cells, an equal number of lymphocytes, and histiocytes infiltrating into the blood vessels in the superficial dermis. The dermal papilla and superficial dermis also showed uniformly reddish masses stained with crystal violet confirming amyloid deposits (Figure 1E and F).

Case 2: The biopsy of the right leg revealed epidermal hyperkeratosis, irregular hyperplasia of the spinous layer, increased basal pigment cells, red mass material deposition in the dermal papilla, and superficial perivascular lymphatic and histiocytic infiltration. Crystal violet staining was positive for amyloid bodies (Figure 2E and F).

Case 3: The LA lesions are usually located primarily on the shins or other extensor aspects of the extremities; the thighs, the upper back, abdominal area, and chest wall may also be involved[1,2]. While LA is often limited to localized areas of the body, it can present in a generalized fashion[3]. Due to the atypical presentation and the lack of age-specific distribution of lesions for the diagnosis of AD, a skin biopsy was performed on the back skin to aid in the diagnosis. Pathological findings included hyperkeratosis with incomplete keratosis and irregular hyperplasia of the spinous layer. Moreover, a pink, amorphous material can be seen in the dermal papilla. Crystal violet staining was positive for amyloid deposits (Figure 3E and F).

Case 4: A biopsy specimen obtained from a papular lesion of the right shin revealed hyperkeratotic and hyperplastic epidermis and homogeneous pinkish materials in the dermal papilla. Crystal violet staining was positive for amyloid deposits (Figure 4E and F).



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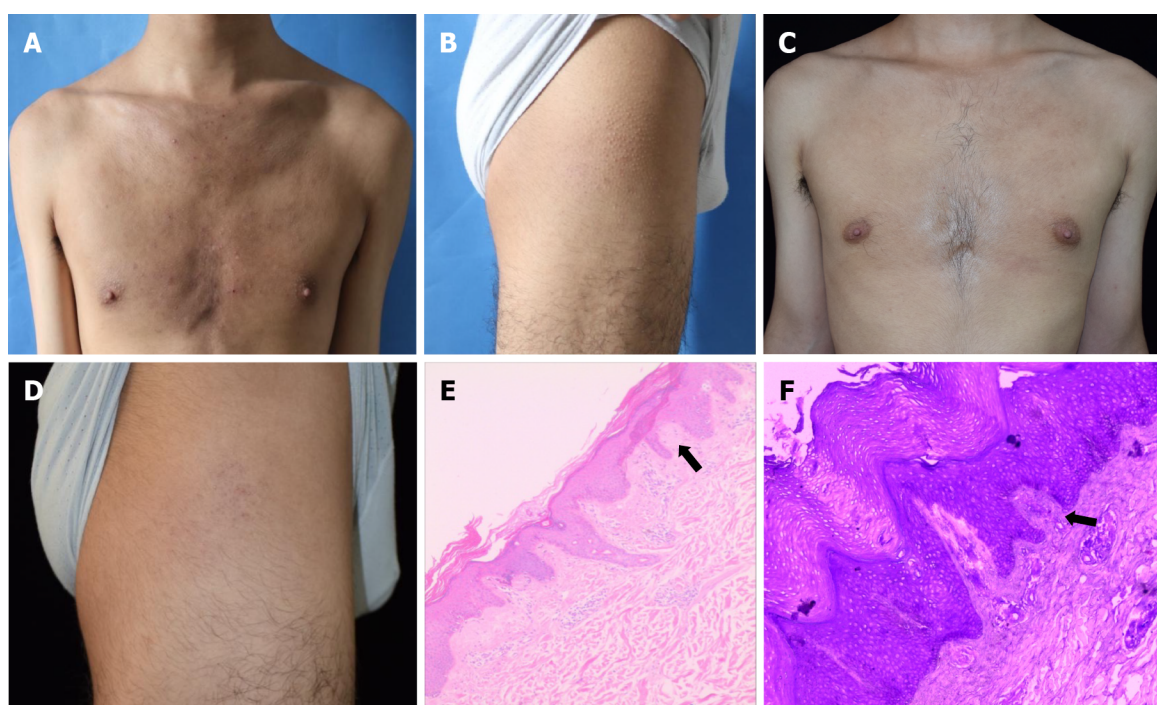
Figure 2 Case 2. A and B: Dense distribution of hard brown papules was observed on both lower limbs, with scales on the surface and dry and rough skin at baseline. Moreover, post-inflammatory hypopigmentation was evident on the anterior aspects of the calves; C and D: After 16 wk of treatment, the rash on both lower limbs was markedly reduced, the papules became flat, the scales were reduced, and the skin became smooth. Furthermore, the rippled appearance of the lesions of the posterior thighs has considerably diminished after the treatment, suggesting a decreased burden of amyloid deposits; E: Histopathological examination revealed epidermal hyperkeratosis, irregular hyperplasia of the spinous layer, increased basal pigmented cells, and red mass material deposition in the dermal papilla (hematoxylin & eosin staining, $\times 100$); F: Crystal violet staining was positive for amyloid bodies (crystal violet staining, $\times 400$). The arrow indicates amyloid deposits.

Initial diagnosis

Case 1: The patient had the following essential features for the diagnosis of AD based on the American Academy of Dermatology (AAD) diagnostic criteria 2014 including: Pruritus and a history of chronic and relapsing eczema. Besides, supporting features for the diagnosis of AD consisted of a personal history of allergic rhinitis, immunoglobulin E reactivity, and xerosis. The lesions among AD adults are frequently localized to the extremities; however, the lesions of this patient were generalized and involved the whole body. According to the eczema area and severity index, the severity of AD in this patient was estimated to be very severe, with a score between 7.1 and 21 denoting moderate, 21.1 to 50 indicating severe, and 50.1 to 72 designating very severe. Thus, the patient was considered to have concurrent refractory LA and AD.

Case 2: The patient had the following essential features for the diagnosis of AD based on the AAD diagnostic criteria 2014: Pruritus and a history of a chronic and relapsing eczema, with typical morphology and age-specific patterns. In addition, supportive features included a personal history of allergic rhinitis and xerosis. Thus, a diagnosis of LA coexisting with chronic AD was made.

Case 3: Important supportive features included a personal history of allergic rhinitis, early age of onset, immunoglobulin E reactivity, and "goose bump" appearance on thighs and xerosis. A diagnosis of LA associated with chronic AD was made based on the clinical and histopathological findings.



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Figure 3 Case 3. A and B: Dense distribution of hard brown papules was observed on the chest plus papules on the thighs, with a "goose bump" appearance presenting at baseline, suggestive of atopic dermatitis; C and D: After 16 wk of treatment, the rash on the lower limbs markedly improved, and the papules were reduced and became flat; E: Histopathology revealed hyperkeratosis with incomplete keratosis and irregular acanthosis. Further, a pink amorphous material can be seen in the dermal papilla (hematoxylin & eosin staining, $\times 100$); F: Crystal violet staining was positive for amyloid (crystal violet staining, $\times 400$). The arrow indicates amyloid deposits.

Case 4: The patient had the following essential features: Pruritus and a history of chronic and relapsing eczema, with typical morphology and age-specific patterns. Other important characteristics were a family history of allergic conjunctivitis and xerosis. Based on these findings, the patient was diagnosed with LA associated with chronic AD.

FINAL DIAGNOSIS

LA coexisting with AD.

TREATMENT

Case 1

Previous treatments with topical corticosteroids and an antihistamine had not produced any apparent improvement; thus, we administered dupilumab injection subcutaneously at a dose of 600 mg for the first time and 300 mg every 2 wk thereafter.

Case 2

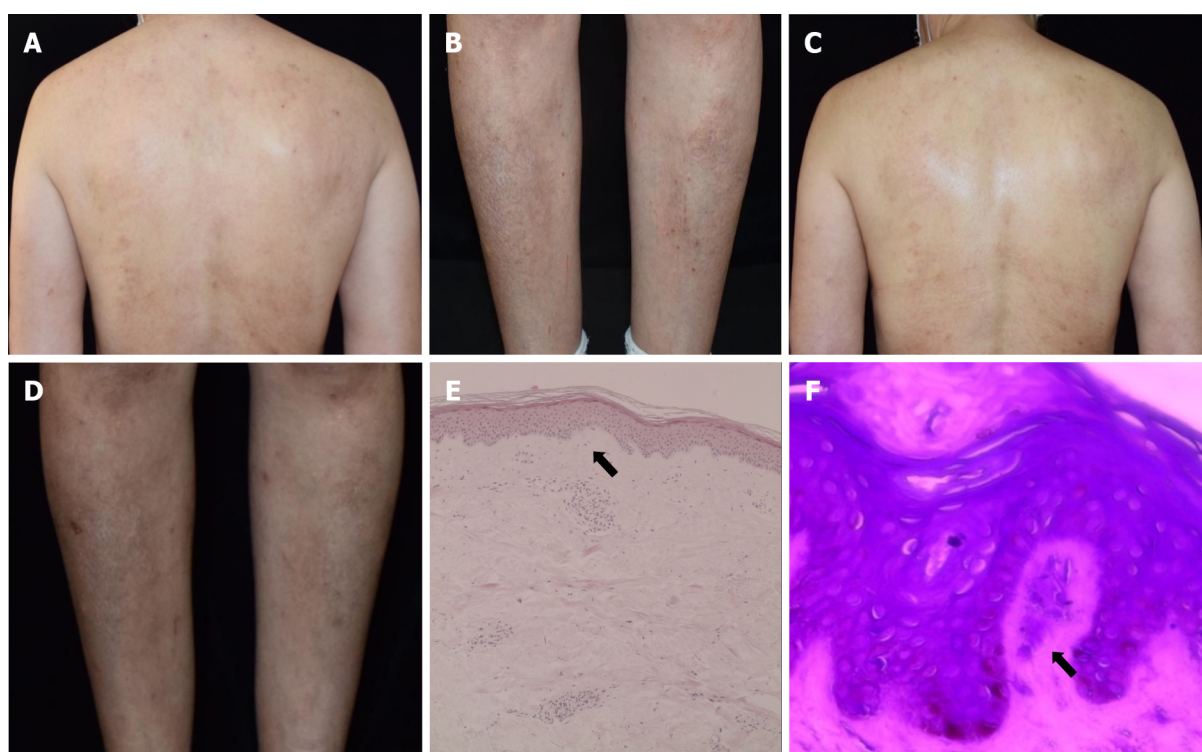
Treatment was then initiated with dupilumab at a dose of 600 mg, which was injected subcutaneously, and continued at a dose of 300 mg every 2 wk thereafter.

Case 3

The patient started on subcutaneous injection of dupilumab at a dose of 600 mg for the first time and 300 mg every 2 wk thereafter.

Case 4

We decided to treat the patient's lesions with subcutaneous injections of dupilumab at a dose of 600 mg initially, which was continued at a dose of 300 mg every 2 wk thereafter.



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Figure 4 Case 4. A and B: Erythema and a dense distribution of hard brown papules were seen on the patient's back. Both calves showed a characteristic rippled pattern, which was most prominent on the anterolateral aspect of the right calf; C and D: After 16 wk of treatment, the papules on both calves became flat and the wavy pattern markedly disappeared, suggestive of diminished amyloid burden; E: Hyperkeratotic and hyperplastic epidermis as well as homogeneous pinkish materials in the dermal papilla were seen (hematoxylin & eosin staining, $\times 100$); F: Crystal violet staining was positive for amyloid deposits (crystal violet staining, $\times 400$). The arrow indicates amyloid deposits.

OUTCOME AND FOLLOW-UP

Case 1

After 16 wk of treatment, the plaques steadily flattened and decreased in size and number, and the skin became smooth. The itching continued to improve without any obvious adverse reactions. The patient continues to receive dupilumab maintenance therapy by injection of 300 mg every 4 wk.

Case 2

After 16 wk of treatment, the patient had experienced complete resolution of pruritus. He had visual clinical improvement of his skin lesions with steadily flattening and lightening of the papules and plaques. No obvious adverse reactions were observed.

Case 3

At week 16, the patient showed a marked reduction of pruritus, and subsequent progressive improvement of both AD and LA.

Case 4

After 16 wk of treatment, the papules steadily flattened and decreased in number, and the itching disappeared. Moreover, no obvious adverse reactions were observed. She is still under treatment.

DISCUSSION

LA has been implicated to be associated with other skin conditions including lichen planus and especially AD[4]. It is also associated with HIV, Type A multiple endocrine tumor, vascular lymphoid hyperplasia with eosinophilia, ankylosing spondylitis, autoimmune thyroiditis, hyperthyroidism, and other autoimmune disorders[5-7]. LA treatment is generally directed to relieve pruritus and inflammation, such as low doses of systemic cyclosporine, topical corticosteroids, and oral retinoids such as acitretin. Owing to the drying effects of retinoid on the skin and thereby the potential for exacerbation of AD, the therapeutic options for treating co-existing LA and AD are more limited than those for LA alone.

[8]. Successful treatment of AD-associated LA with oral cyclosporine and subsequent narrow band ultraviolet B therapy has been reported[9]. Three cases of LA with AD have also been successfully treated with CO₂ laser[10]. Koh *et al*[8] also reported a case of LA with AD successfully treated with alitretinoin, which has lower mucocutaneous side-effects, as compared to other vitamin A derivatives.

Aoki *et al*[11] reported a case of generalized LA with AD in a female patient, whose intractable pruritus decreased within 4 wk after treatment with dupilumab, her eczematous lesions significantly improved, and the LA papules flattened and decreased after 3 mo of treatment. Humeda *et al*[12] reported a case of generalized PCA in a male patient without an atopic disease history who had a 4-year history of severe itching. After treatment with dupilumab, both itching and rash were markedly improved. An excellent response to dupilumab was observed in the treatment of extensive LA associated with AD in our patients. No adverse effect or relapse till date was observed. Thus, dupilumab should be considered more often in the treatment of extensive, recalcitrant cases of LA associated with AD. The pathogenesis of PCA is still not clearly established, but it is considered to involve both genetic and environmental factors. Frictional epidermal damage, apoptosis, viral infection, and other triggers have been implicated in the disease etiology in previous reports. Chronic irritation, itching, and scratching causing prolonged epidermal trauma may lead to dermal amyloid deposition by inducing degradation of keratinocytes, thereby leading to amyloid formation by dermal macrophages and fibroblasts through conversion of keratin peptides to amyloid fibrils that react with antikeratin antibodies[13,14]. Thus, scratching seems to be the most important step in its pathogenesis. Hence, treatment modalities should be centered on minimizing skin trauma and relieving pruritus. A previous study has suggested that small fiber neuropathy and interleukin (IL)-31 receptor overexpression may play a role in the intense pruritus associated with PCA[11]. IL-31, a key mediator of pruritus, signals through a receptor composed of two subunits, IL-31 receptor A and oncostatin M receptor β (OSMR β). A familial study of some cases of PCA has revealed mutations in both genes encoding the subunits of IL-31 receptors (IL31RA and OSMR β)[15]. It has been demonstrated that IL-4, IL-13, and IL-31 are associated with sensory nerve sensitization and itching in AD patients, leading to scratching that further exacerbates inflammation and barrier dysfunction[16]. IL-31 is significantly overexpressed in the skin samples of patients with AD. Thus, it is possible that the IL-31 signaling pathway is involved in the pathogenesis of both PCA and AD, and patients with abnormalities in this pathway may show phenotypes of both diseases[7].

Dupilumab, a human anti-IL-4 receptor- α monoclonal antibody that blocks signaling of both IL-4 and IL-13[17], has been approved by the Food and Drug Administration for use in the treatment of adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical medications or when those therapies are not advisable. Previous analyses have shown that treatment with dupilumab normalizes the AD transcriptome by downregulating markers of type 2 inflammation such as IL-13 and IL-3. It effectively treats itching by directly blocking IL-4 and IL-13 on sensory neurons and indirectly through inhibition of IL-31 production by T2-helper cells by blocking IL-4[18]. We hypothesized that dupilumab may also be effective in treating LA with AD. In our four cases of LA with AD, we observed a convincing antipruritic effect and improvement of skin lesions after injection of dupilumab. The advantages of this treatment are practicability, convenience, and low side-effects. In general, AD symptomatology and distribution depend on the patient's age at the time of presentation. Adults may present with dry and scaly patches on the extremities[19]. Our cases demonstrated that dupilumab may be a good therapy for LA coexisting with AD regardless of the generalized eczema type or typical age-specific patterns of clinical phenotypes of adult AD.

CONCLUSION

Dupilumab may shed light on the systematic treatment of refractory LA patients associated with AD but further case studies are required to evaluate the effectiveness of this drug for these cases. Meanwhile, the mechanism by which dupilumab improves LA remains elusive but it seems that the interruption of the vicious cycle of pruritus and skin trauma as well as its direct and indirect effects on the cytokines involved in the pathophysiology of this disorder are all implicated.

FOOTNOTES

Author contributions: Gao BQ and Zhang JF performed the pathological studies, laboratory testing, and clinical data collection; Zhu Q and Shi LP were responsible for patient care and drafted this manuscript; Zhang GQ revised the manuscript critically for important intellectual content; all authors contributed to the article and approved the submitted version.

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