interactions are crucial for these responses.

Although these studies strongly supported the hypothesis that anti-hCOL17 IgG autoantibodies in BP patients have pathogenic activity, such activity had not been directly demonstrated in vivo. In 2007, Nishie et al. confirmed this hypothesis by using the unique technique of "humanization of autoantigen".[31] First, they generated murine *Col17*-knockout (m*Col17*$^{-/-}$) mice that developed blisters and erosions on the skin, symptoms that reproduce the human disease non-Herlitz epidermolysis bullosa, which is caused by null mutations in the *COL17A1* gene. By crossing Col17 knockout mice with hCOL17-expressing Tg mice, COL17-humanized (*hCOL17*$^{+/+}$, *mCol17*$^{-/-}$) mice were generated. Those COL17-humanized mice lack mCol17 but express hCOL17. Neonatal COL17-humanized mice were passively transferred with BP-IgG, which produced diffuse erythema and epidermal detachment by gentle skin friction associated with dermal-epidermal separation and inflammatory cell infiltration of neutrophils and lymphocytes (Fig. 3a,b). Direct IF showed linear deposition of human IgG and murine C3 at the DEJ (Fig. 3c,d), which simulates the human BP phenotype. This passive-transfer neonatal mouse model was the first to directly show the pathogenicity of BP-IgG in vivo.

Some studies focusing on complement activation have been performed using a

neonatal COL17-humaized BP mouse model. Wang et al. generated recombinant Fab fragments against hCOL17 NC16A from antibody repertoires of BP patients using a phage display method.[32] Complement activation is considered to be critical for blister formation in neonatal BP model mice.[26] Some of the recombinant Fab fragments showed marked ability to inhibit the binding of BP autoantibodies to hCOL17 and to inhibit subsequent complement activation in vitro. Those recombinant Fabs also prevented the binding of anti-COL17 NC16A antibodies to the NC16A domain in neonatal COL17-humanized mice and inhibited complement activation. Li et al. recently generated a recombinant IgG1 monoclonal antibody against hCOL17 NC16A that can reproduce the BP phenotype in the neonatal COL17-humanized mise.[33] They introduced alanine substitutions at various C1q binding sites of the Fc region of the monoclonal antibody. Those mutated IgG antibodies failed to activate the complement in vitro and drastically lost pathogenic activity in neonatal COL17-humanized mice.[33] These two studies indicate that antibody-dependent complement activation is necessary for blister formation in neonatal BP model mice.

Those passive-transfer animal models demonstrate only transient disease activity. Recently, an active BP mouse model that continuously produces pathogenic IgG in vivo and that stably demonstrates the BP phenotype has been developed using

immunodeficient *Rag-2*$^{-/-}$/COL17-humanized mice.[34] Adoptive transfer of splenocytes from wild-type mice immunized by the grafting of hCOL17-expressing Tg mouse skin into *Rag-2*$^{-/-}$/COL17-humanized mice induced continuous production of anti-hCOL17 IgG and blister formation corresponding to the clinical, histological and immunopathological features of BP (Fig. 4). This study also demonstrated that $CD4^+$ T cells are crucial for the development of the BP phenotype in the active BP model.[34] In human BP, the presence of autoreactive $CD4^+$ T cells has been reported, indicating the pathogenic role of $CD4^+$ T cells in producing BP.[35-37] High frequencies of particular MHC class II alleles have been also reported.[38] These findings indicate that the autoreactive $CD4^+$ T cells may be activated through the interaction of the specific MHC class II molecule in BP.

Studies on IgE antibodies against COL17

Not only IgG but also IgE autoantibodies against COL17 are considered to be pathogenic in BP patients.[39] The early urticarial phase of the eruptions seen in BP seems to be associated with IgE, that is based on the common knowledge of IgE-mediated degranulation of mast cells in allergic forms of urticaria.[40] Total IgE levels are elevated in 70% of untreated BP patients and IgE autoantibodies against COL17 are detected in

86% of untreated BP patients.[41] Iwata *et al.* reported that the existence of IgE autoantibodies against COL17 relates to a severe form of BP.[42] BP patients with IgE against COL17 require a longer period of treatment for remission, greater amounts of corticosteroids and more intensive treatments for remission.[42] These findings suggest that IgE autoantibodies against COL17 are associated with BP pathogenesis and disease activity.

The passive-transfer models for BP using IgG against COL17 do not induce the eosinophil infiltration that is a characteristic finding in human BP.[25, 31] Zone et al. successfully reproduced the itchy erythematous lesions in engrafted human skin in SCID mice using IgE antibodies against LABD97, a component of the shed ectodomain of hCOL17, which are generated with IgE hybridoma to the LABD97 antigen.[43] The hybridoma was injected subcutaneously in SCID mice engrafted with human skin, and they produced IgE antibodies against LABD97 in vivo. The IgE bound to the DEJ of the engrafted human skin and induced erythema. Then, all the injected mice developed severe eosinophil infiltration and mast cell degranulation within the grafts and most of them developed histological, but not clinically detectable, subepidermal blisters. This BP model induced by IgE antibodies reproduces the clinical and histological findings of human BP lesions including eosinophil infiltration.

Fairley et al. developed an experimental BP mouse model using IgE autoantibodies from BP patients.[44] They isolated total IgE from BP sera and injected it into human skin grafted onto athymic nude mice. Elevated erythematous plaques similar to early-stage BP lesions developed in all the human skin grafts after injection of the BP-IgE. Histological examination of the lesions revealed the engorgement of blood vessels and a dermal inflammatory infiltrate composed of neutrophils, eosinophils, and degranulated mast cells. Higher doses of BP IgE autoantibodies induced histological dermal-epidermal separation in the grafts. This study provided direct evidence of a pathogenic role for IgE autoantibodies in BP. More recently, they reported a case of steroid-unresponsive BP that was successfully treated with omalizumab, a humanized monoclonal antibody that inhibits IgE binding to the high-affinity receptor FcεRI,[45] suggesting that IgE autoantibodies could be a new therapeutic target in BP.

Summary

Recent studies using animal models have demonstrated the pathogenicity of IgG and IgE antibodies against COL17 as well as the subsequent immune responses, such as complement activation, mast cell degranulation, and infiltration of inflammatory cells, including of neutrophils and/or eosinophils, although some of these responses seem to

remain controversial. Moreover, in vitro studies of COL17 protein reveal the precise mechanisms of dermal-epidermal separation. The autoreactive $CD4^+$ T lymphocytes which probably serve as a commander of autoimmune reactions in BP should be further investigated, because they are a potential therapeutic target in BP.

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Figure legends

Fig. 1

Clinical, histological and direct immunofluorescence (IF) features of BP. Tense blisters and erosions develop in itchy edematous erythema on the thighs (*A*). Histopathological finding in a skin specimen taken from a tense bulla. Subepidermal blister formation associated with dermal inflammatory cell infiltration mainly of eosinophils and lymphocytes (*B*). Direct IF of lesional skin demonstrates linear deposition of IgG at the dermal-epidermal junction (*C*). Indirect IF using 1M sodium chloride split skin as a substrate shows linear deposition of IgG on the roof side of the separation at the dermal-epidermal junction (*D*).

Fig. 2

Schemas of the COL17 molecule in vivo. COL17 is a type II transmembrane protein that spans the lamina lucida and projects into the lamina densa of the epidermal basement membrane zone. The extracellular domain of COL17 has at least one loop structure in the lamina densa in vivo (*A*). The extracellular region of COL17 involves 15 collagenous domains separated from one another by noncollagenous domains. The noncollagenous 16A (NC16A) domain, located at the membrane-proximal region of

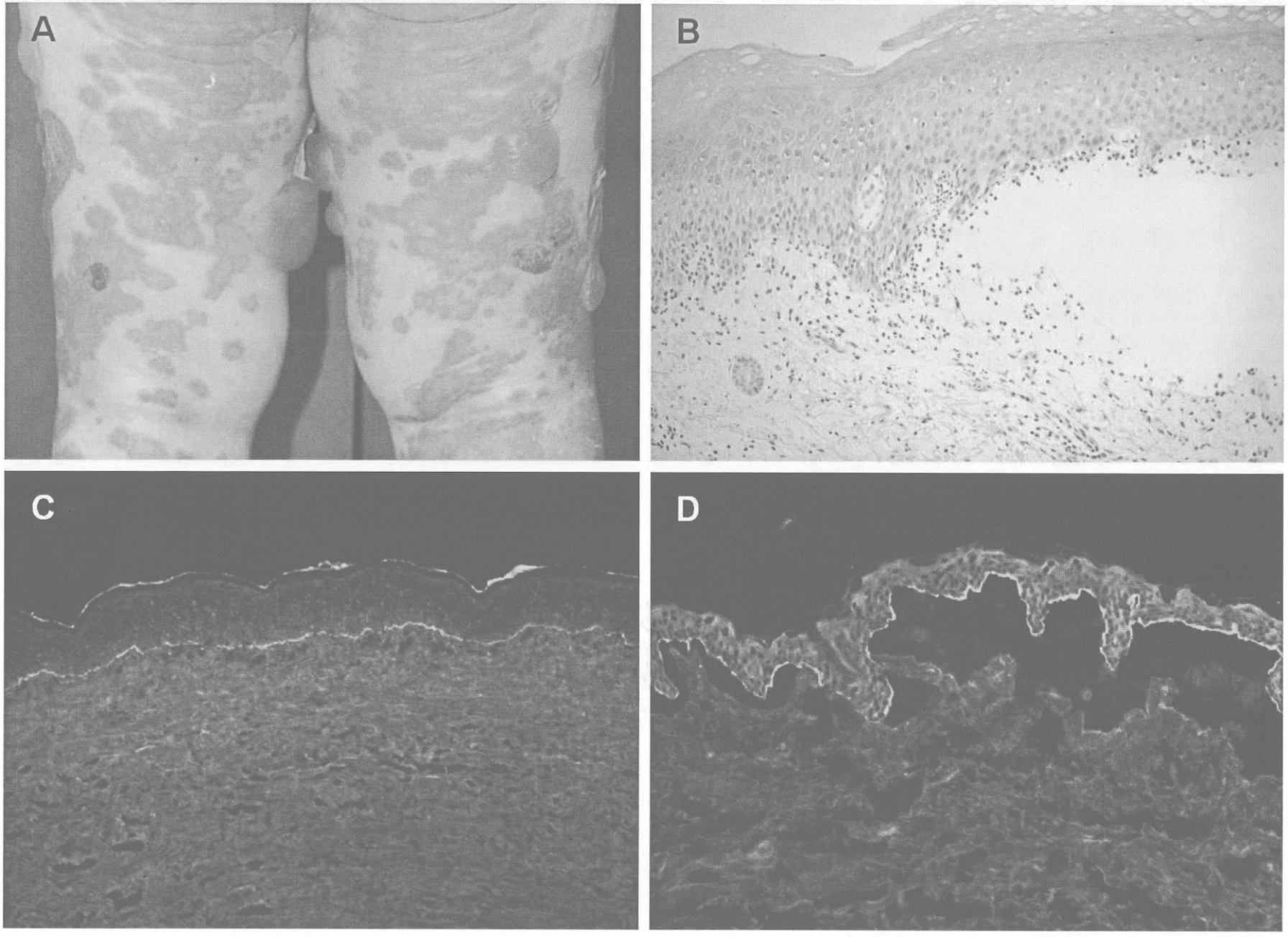
COL17, is considered to be the major pathogenic epitope for bullous pemphigoid (*B*).

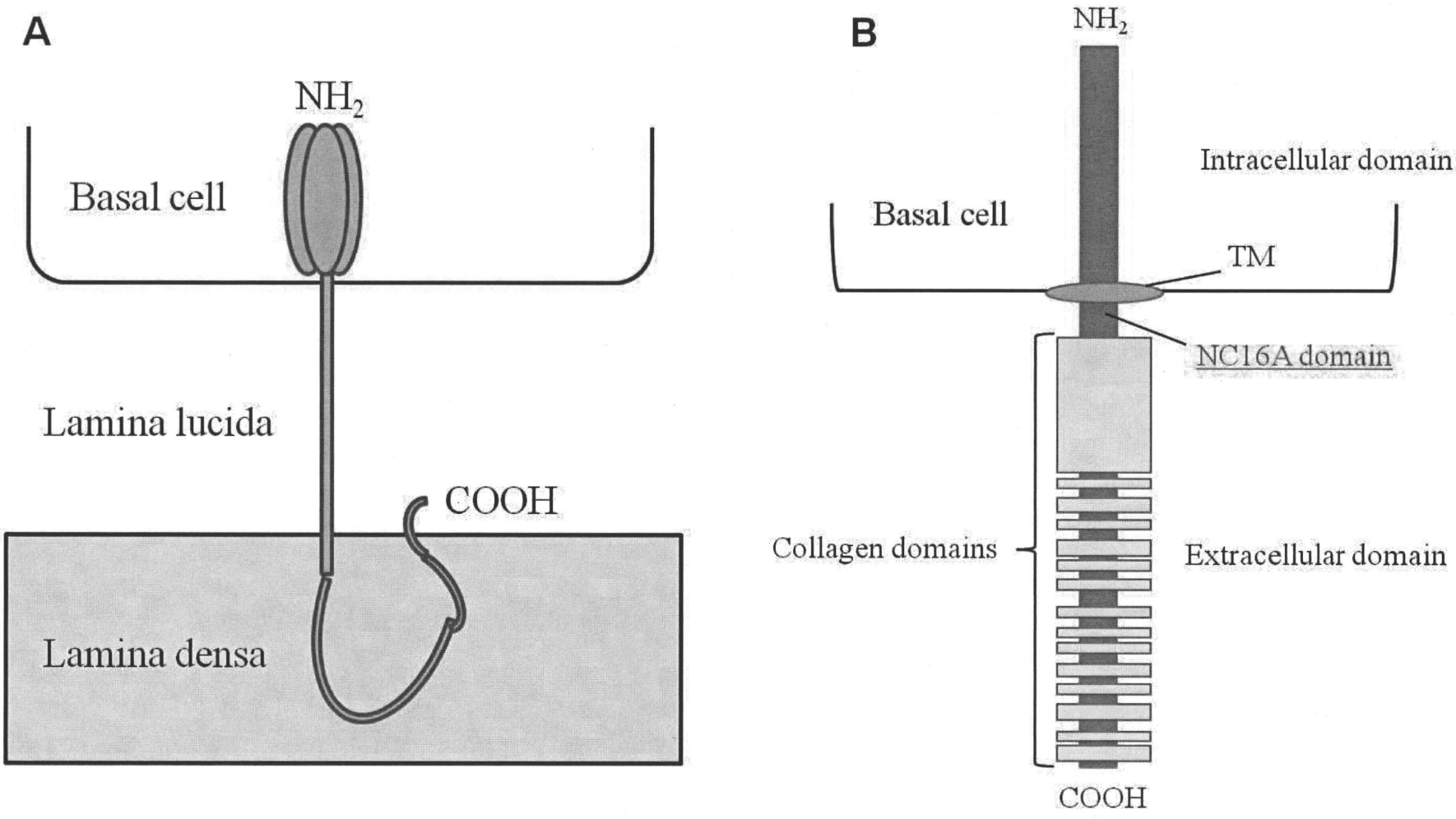
Fig. 3

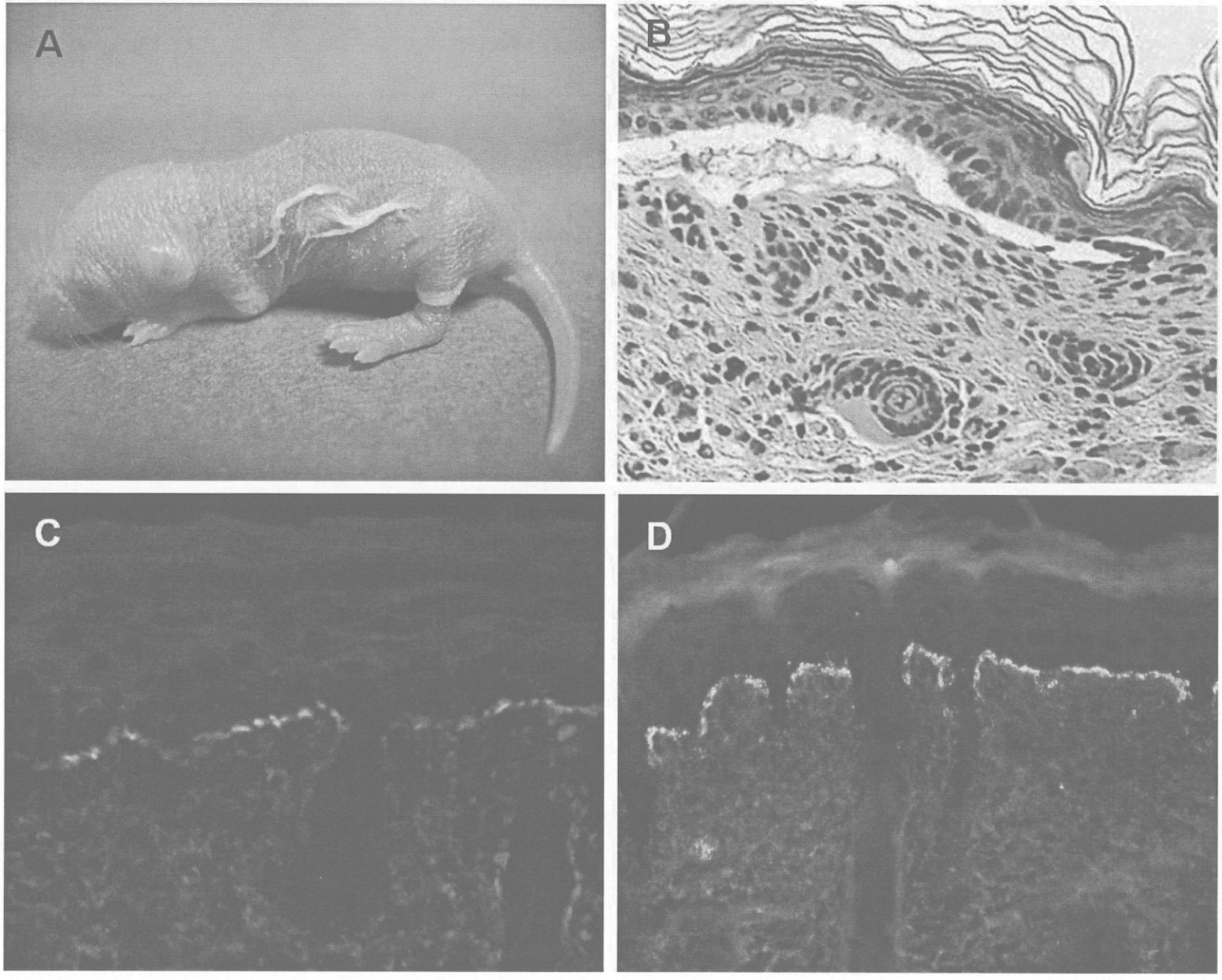
A passive-transfer neonatal BP model using the COL17-humanized mouse. The neonatal COL17-humanized mouse that was passively transferred with IgG affinity-purified against hCOL17 NC16A from BP patients shows epidermal detachment by gentle skin friction at 48 hours after transfer (*A*). Lesional skin specimen demonstrates dermal-epidermal separation and infiltration of inflammatory cells, including neutrophils and lymphocytes (*B*). Direct IF reveals linear deposition of human IgG (*C*) and murine C3 (*D*) at the dermal-epidermal junction.

Fig.4

Clinical, histological and direct IF features of an active BP mouse model. *Rag-2*$^{-/-}$/COL17-humanized mice given immunized splenocytes demonstrate large patches of hair loss associated with erythema, and erosions and crusts on the trunk and paws (*A*). Spontaneously developing blisters are also observed in the recipients (arrow) (*B*). Epidermal detachment by gentle friction on the trunk is observed (*C*). Histological examination of diseased mice reveals separation between dermis and epidermis with mild inflammatory-cell infiltration (*D*). Direct IF of lesional skin biopsy reveals linear deposition of mouse IgG (arrows) (*E*) and mouse C3 (arrows) (*F*) at the DEJ.


A
B
C
D


A
NH2
Basal cell
Lamina lucida
COOH
Lamina densa
B
NH2
Intracellular domain
Basal cell
TM
NC16A domain
Collagen domains
Extracellular domain
COOH


A
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A
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Case Report

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Pyoderma Gangrenosum of the Eyelid: Report of Two Cases and Review of the Literature

N. Saito[a] T. Yanagi[a] M. Akiyama[a] H.Y. Lin[a] S. Kasai[a] Y. Fujita[a] N. Yamane[a]
D. Inokuma[a] S. Kase[b] K. Ono[c] H. Minakawa[d] H. Shimizu[a]

Departments of [a]Dermatology, [b]Ophthalmology and [c]Plastic Surgery, Hokkaido University Graduate School of Medicine, and [d]Department of Plastic Surgery, Hokkaido Cancer Centre, Sapporo, Japan

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Pyoderma gangrenosum · Eyelid

Abstract
Pyoderma gangrenosum (PG) of the eyelid is extremely rare, and its proper management is essential for the preservation of visual function. Here, we report 2 cases of PG of the eyelid with intraorbital involvement. In both cases, the skin and intraorbital lesions improved after systemic immunosuppressive therapies; however, corneal perforation occurred in 1 case. In order to assess the clinical features of PG of the eyelid and to obtain clues for optimal treatment, we reviewed 15 well-documented cases in the literature, including the present cases. Corneal perforation occurred in 4 cases and defective ocular motility in 1 case. Three patients eventually underwent enucleation of the affected eye. Our cases and the literature review clearly indicate that MRI is a powerful tool for evaluating the extent of extracutaneous PG lesions around the eye and that early diagnosis and immediate immunosuppressive therapy are crucial for the preservation of visual acuity.

Introduction

Pyoderma gangrenosum (PG) is a destructive and necrotising skin disease characterised by neutrophilic infiltration. PG lesions have a predilection for the lower extremities and trunk although they can occur at any site [1]. PG of the eyelid is extremely rare and the clinical features, prognosis and optimal treatments have yet to be fully described. In order to clarify the characteristics of PG affecting the eyelid and to obtain clues as to the most efficient treatment, we report 2 cases and review 13 well-documented cases in the literature.

Case Reports

Case 1

A 75-year-old Japanese man was referred to our department with a two-year history of recurrent ulcers on his right upper eyelid. Two and a half years before his visit, a twig had stuck into the upper right eyelid. The painful wound had gradually enlarged and become an eroding ulcer. The lesion was suspected to be an adnexal tumour by plastic surgeons. However, neither repeated surgical operations nor antibiotic administration improved the ulcer on the eyelid. Initial physical examination at our outpatient clinic showed an eroding ulcer extending from the right upper eyelid to the right cheek along the surgical operation wound. The ulcer on the right upper eyelid involved the superior tarsus, resulting in a lagophthalmos (fig. 1a, b). Skin biopsy specimens from the edge of the ulcer on the right cheek showed dense neutrophil infiltration (fig. 1c, d). Light microscopic observations did not show giant cells, ballooning degeneration or reticular degeneration. Negative results for Gram, PAS, Grocott and Ziehl-Neelsen stains, culture of skin tissue or polymerase chain reaction analyses failed to indicate any infectious diseases with bacteria, mycobacteria, atypical mycobacteria and fungi. Neither the Tzanck test nor immunofluorescence studies of herpes viral antigens showed any herpes virus infection. In laboratory examination, neither anti-proteinase 3, anti-myeloperoxidase antibodies nor atypical anti-neutrophil cytoplasmic antibodies were detected. From these clinical features and histopathological findings, we diagnosed the ulcers as PG.

Detailed examination failed to detect any systemic complications including inflammatory bowel diseases, haematolog-

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Nao Saito, MD
Department of Dermatology
Hokkaido University Graduate School of Medicine
N15 W7, Sapporo 060-8638 (Japan)
Tel. +81 11 716 1160, Fax +81 11 706 7820, E-Mail bird09160078@yahoo.co.jp

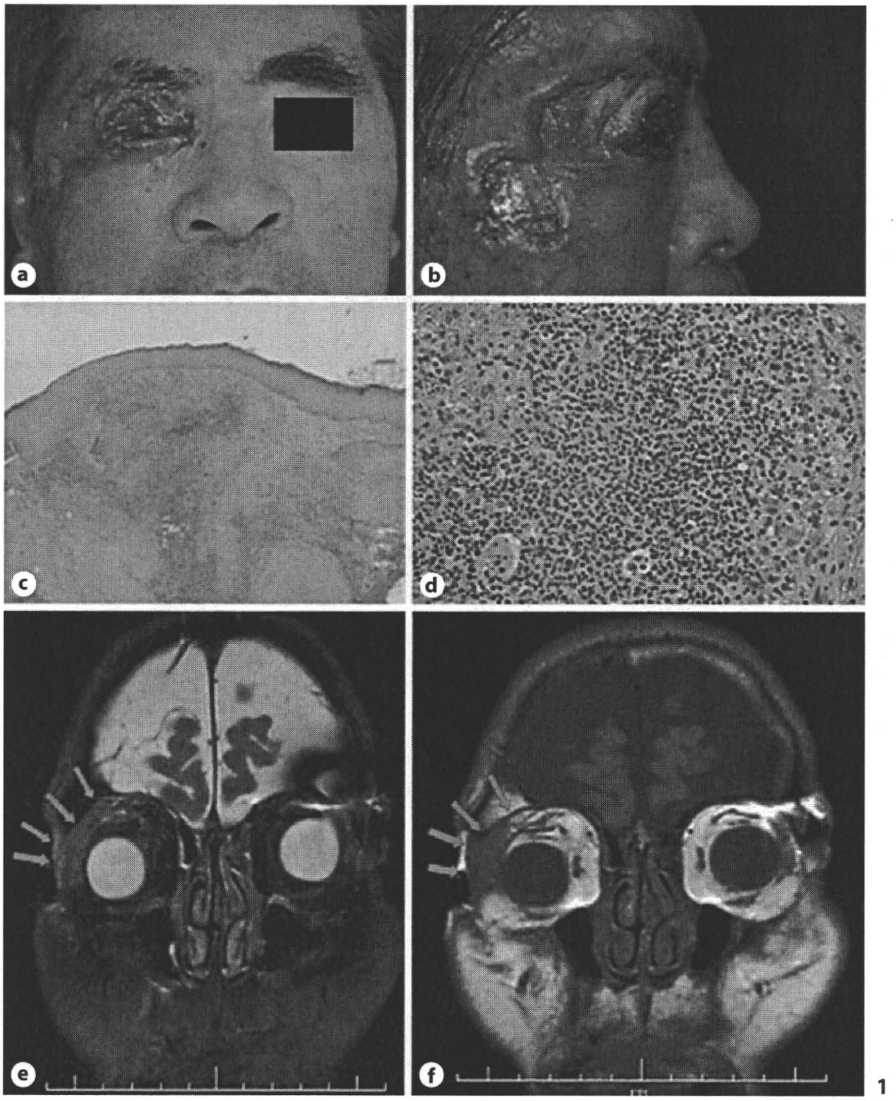

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Fig. 1. Clinical, histopathological and MRI features of case 1. **a**, **b** An eroding ulcer extended from the right upper eyelid to the right cheek along the surgical operation wound margin. **c**, **d** Skin biopsy specimens from the edge of the ulcer on the right cheek showing dense neutrophil infiltration. HE. Original magnifications: ×20 (**c**), ×60 (**d**). **e**, **f** Orbital MRI showing homogeneous hyperintensity on fat-saturated T_2-weighted image (**e**, red arrows) and hypointensity on T_1-weighted image in the right lachrymal gland and upper eyelid (**f**, red arrows), indicating acute inflammation.

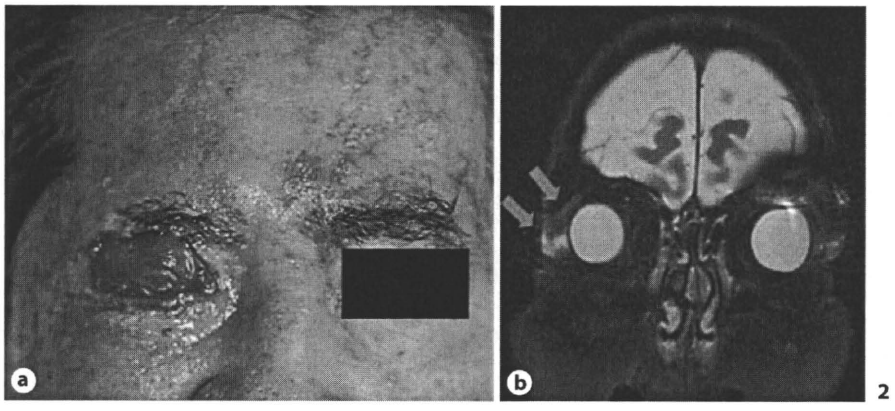

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Fig. 2. Clinical and MRI features of case 1 after PG remission. **a** The eroding ulcer healed with scarring. Corneal opacity appeared. **b** Orbital, fat-saturated T_2-weighted image after 4 months of immunosuppressive therapy showing that the hyperintense area had diminished (red arrows).

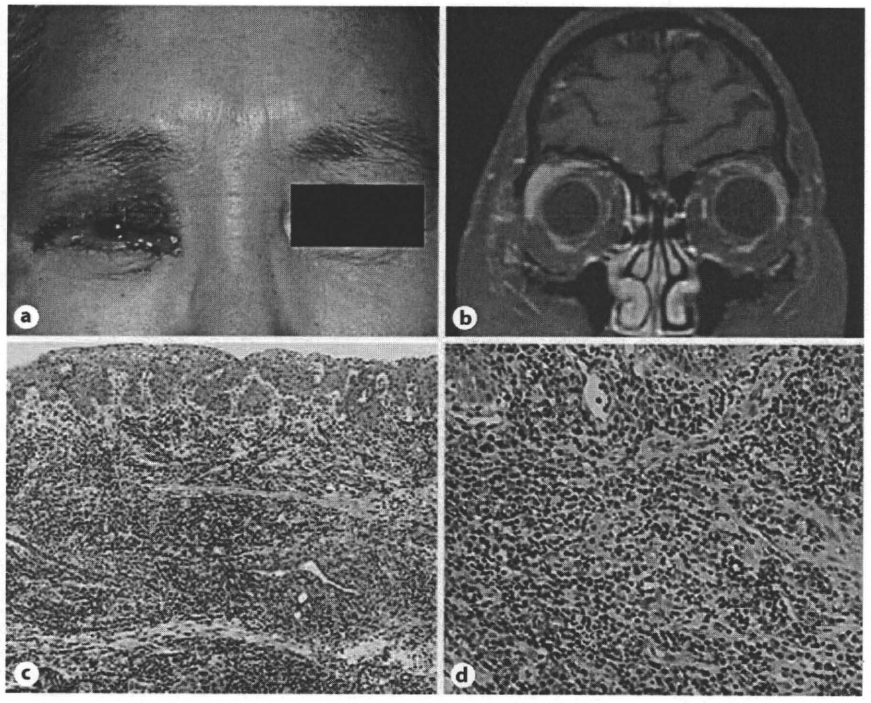

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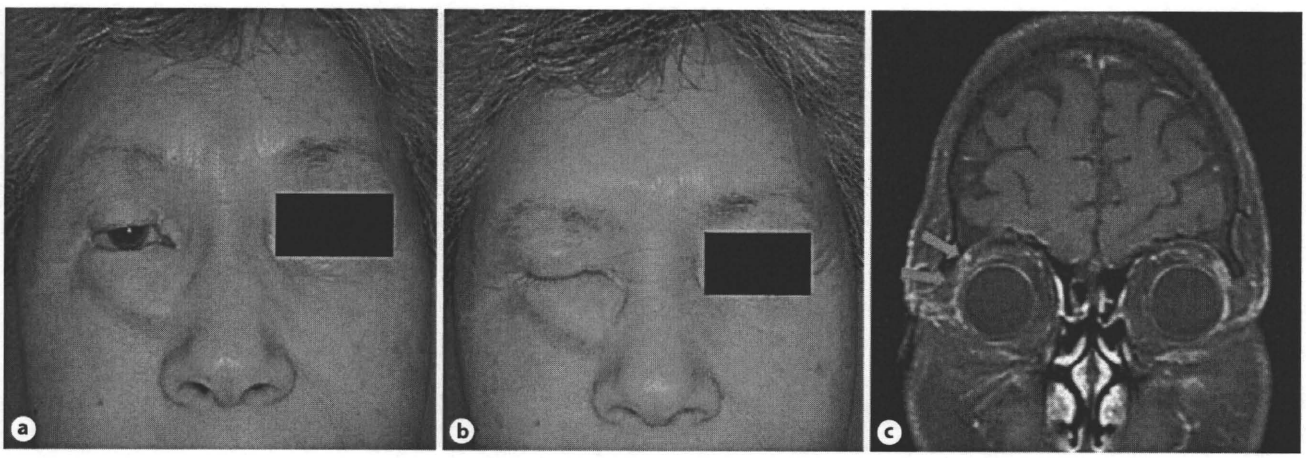
Fig. 3. Clinical, histopathological and MRI features of case 2. **a** An ulcer with surrounding erythema on the right upper eyelid. **b** Orbital MRI showing area of hyperintensity on T_1-weighted image in the right lachrymal gland and upper eyelid. **c**, **d** Skin biopsy specimens showing dermal abscesses with dense aggregates of plasma cells. HE. Original magnifications: ×20 (**c**), ×60 (**d**).

Fig. 4. Clinical and MRI features of case 2 two years after the eyelid repair operation. She was able to open (**a**) and close her eyes (**b**). **c** Orbital fat-saturated T_1-weighted image after immunosuppressive therapy revealing the area of hyperintensity had diminished (red arrows).



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ical disorders or rheumatoid arthritis. Orbital MRI showed homogeneous hyperintensity areas on fat-saturated T_2-weighted image, and hypointensity areas on T_1-weighted image in the right lachrymal gland and upper eyelid (fig. 1e, f), suggesting an acute inflammation of the extracutaneous areas. An initial combined therapy with prednisolone (1 mg/kg/day) and cyclosporin A (5 mg/kg/day) improved the skin lesions as well as intraorbital involvement (fig. 2a, b). PG disease activity was controlled and the eroding ulcer on the upper portion of the right eyelid and cheek healed with scarring. However, the destruction of the right eyelid led to poor eye closure and continuous corneal exposure to air. Two months after the remission of the cutaneous lesions of PG, perforation of the right cornea occurred and the right eye had to be enucleated. Treatment with prednisolone and cyclosporin A was continued and no recurrence was observed for 4 months after the enucleation of the eye.

Case 2

A 65-year-old Japanese woman was referred to our department with a 9-month history of a facial ulcer. A painful erythema and ulcer appeared on her right upper eyelid without any preceding episodes. At first, the patient visited an ophthalmology clinic. The lesion was initially diagnosed as

Table 1. Summary of the clinical information on reported cases with PG of the eyelid

Patient No.	Age, years	Sex	Distribution of PG	Initial diagnosis	Initial treatment	Duration from onset to diagnosis	Treatment	Outcome and prognosis	Complications	Ref.
1	64	male	left temple, scleral conjunctivitis, anterior uveitis, corneal opacity	N/A	antibiotics	N/A	PSL, azathioprine	recurrence	arthritis	Happle et al. [2]
2	62	male	left upper eyelid	N/A	N/A	14 days	chlorhexidine gluconate	recurrence	none	Browning et al. [3]
3	63	male	left eye	N/A	N/A	25 years	clofazimine	recurrence	N/A	Mensing [4]
4	67	female	right lower eyelid	N/A	antibiotics	60 days	PSL	recurrence, corneal perforation, evisceration of the eye	diabetic	Newman and Frank [5]
5	80	female	bilateral eyelids	N/A	antibiotics	N/A	PSL	no recurrence	ulcerative colitis	Tirpitz et al. [6]
6	47	female	right lower eyelid, left eyelid	N/A	N/A	8 days	mPSL (500 mg) 3 days, PSL	no recurrence	rhinosinusitis	Sidwell et al. [7]
7	28	female	left upper eyelid, right eye, left orbit, liver, spleen	nodular scleritis, orbital inflammation	N/A	3 years	PSL, cyclosporin	defective ocular motility	arthritis	Miserocchi et al. [8]
8	61	female	right upper eyelid, right necrotising scleritis	chalazia	antibiotics	30 days	PSL, cyclophosphamide	no recurrence	none	Rose et al. [9]
9	56	male	left upper eyelid, ischemic sclerokeratitis, corneal perforation	bacterial infection	antibiotics	14 days	immunosuppressive therapy	eyelid construction, keratoplasty	rheumatoid arthritis	Rose et al. [9]
10	75	female	left upper eyelid	N/A	N/A	a few weeks	PSL	eyelid construction	interstitial pneumonia	Rose et al. [9]
11	67	N/A	lower eyelid, lateral canthus, lateral orbit	N/A	antibiotics	N/A	PSL, clofazimine	corneal perforation, subtotal orbital exenteration	none	Rose et al. [9]
12	82	male	left lower eyelid, left cheek	chronic wound	antibiotics, surgical operation	2.5 years	PSL, cyclosporin	recurrence (after operation)	none	Lindberg-Larsen and Fogh [10]
13	19	female	right lower eyelid	N/A	N/A	N/A	PSL, dapsone	eyelid construction	none	Procianoy et al. [11]
14	75	male	right upper eyelid, lachrymal gland	adnexal tumour	surgical operation	1.8 years	PSL, cyclosporin	corneal perforation, subtotal orbital exenteration	none	present case 1
15	65	female	right upper eyelid, lachrymal gland	chalazia	antibiotics	180 days	PSL	eyelid construction	none	present case 2

N/A = Not available; PSL = prednisolone.