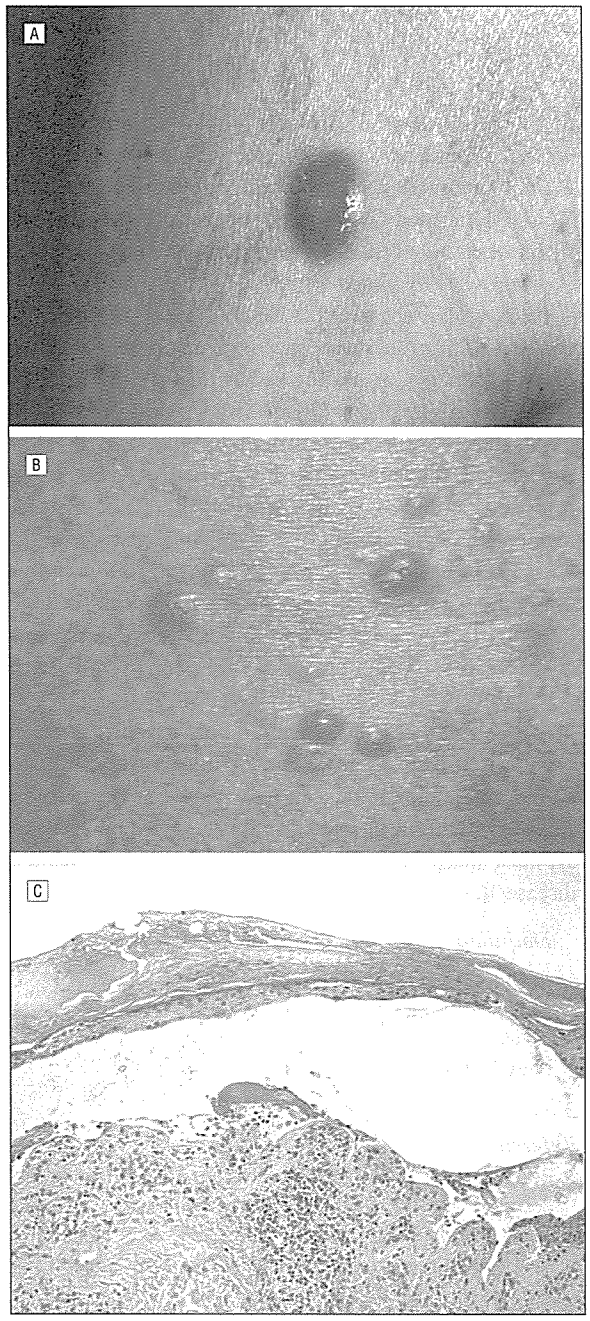

Figure 2. Case 2. A, Indurated tumor on her shoulder. B, Vesicles are scattered over erythrodermic skin. C, Subepidermal bullae are seen with atypical lymphocytes (hematoxylin-eosin, original magnification ×100).

lous lesions. Only 9 cases of vesiculobullous lesions with MF that have been reported have met these criteria.[1] The appearance of MFB in patients with MF is thought to indicate a poor prognosis. The patient in case 2 died within 2 months after the appearance of vesicles, which is a typical clinical course.[1]

The mechanism of blister formation has not been elucidated. Several hypotheses have been proposed: (1) Epidermotropism and accumulation of neoplastic cells in the basal layer of the epidermis may induce the loss of coherence between the basal lamina and the basal keratinocytes. (2) Cytokines released from neoplastic cells may intrude the normal connection between keratinocytes.

Transformed MF, defined as the presence of large cells exceeding 25% of the total lymphoid infiltrate in MF, is rare and associated with poor survival.[2,3] To our knowledge, case 1 is the first example of MFB occurring in a patient with T-MF. Both conditions are thought to be extremely rare and usually have limited survival; therefore, the coexistence of MFB and T-MF is thought to be a rare phenomenon. The relationship between blister formation and T-MF is unclear. While anaplastic large cells in T-MF could release cytokines to induce blistering, the subepidermal blisters in case 1 were observed with MF cells, not anaplastic large cells. Although rare, MFB is regarded as an important clinical subtype of MF.

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Cutaneous Blastomycosis: A Clue for Reassessing the Recent Diagnosis of Pulmonary Sarcoidosis

Blastomyces dermatitidis is an endemic fungus that frequently infects the skin. Herein, we present a case of disseminated blastomycosis initially misdiagnosed as pulmonary sarcoidosis and cutaneous squamous cell carcinoma.

Report of a Case. A 64-year-old man from New Brunswick, the eastern part of Canada, was referred to the dermatology department for a painless verrucous plaque (3.5×1.5 cm) on the helix of his left ear that evolved over the previous 5 months (**Figure 1**). Squamous cell carcinoma was suggested by initial biopsy findings, which showed pseudoepitheliomatous hyperplasia. On analysis of specimens from a second biopsy, multiple broad-based budding yeasts compatible with *B dermatitidis* were disclosed under special staining (**Figure 2**). The diagnosis of cutaneous blastomycosis was further confirmed by positive fungal cultures.

Mono-letter mnemonics in dermatology

A mnemonic is a device or code that helps an individual to memorize key information about something. Many people are using mnemonics in teaching as they have been proven to be a successful learning aid.[1] Recently, we have reviewed the use of mnemonics in dermatologic disorders.[2]

Many websites and books compile lists of mnemonics; thus, there may be more than one mnemonic for a given disorder. It is left to the individual to select one that he or she prefers.

It is not uncommon for individuals to devise their own methods of remembering facts by constructing a word, song, picture, or incident.[2] Self-made mnemonics are often particularly effective, as the time and creative energy devoted to their development result in increased recall.[1]

We wish to point out in this brief communication that using a word or phrase for mnemonics may at times become outdated, similar to a new edition of a book which replaces a previous one. Mnemonics, too, must accommodate new information so that students can reap the maximum benefit from this useful learning aid. Problems can arise when new information is added, because the addition of a letter to the existing word or phrase will ultimately change the composition of a mnemonic that has been in vogue for some time. For instance, the five painful tumors of the skin have been grouped nicely into the word "Bengal" (*b*lue rubber bleb nevus, *e*ccrine spiradenoma, *n*eurilemmoma/neuroma, *g*lomus tumor, *a*ngiolipoma/angioleiomyoma/angiosarcoma, and *l*eiomyoma), or the phrase "blend an egg", but now, with the potential addition of *c*utaneous endometriosis/calcinosis cutis and *o*steoma cutis, its use may be rendered obsolete. The new mnemonic for painful cutaneous nodules is BENGAL CO,[1] where "CO" refers to the first letter of the last two tumors mentioned. In addition, a word or phrase that may be of interest to individuals in some countries, and easily recalled by them, might not be of interest elsewhere or may be difficult for persons in other places to recall.

We wish to highlight that one good technique that can be used in framing mnemonics is a mono-letter. With this technique, it is possible to avoid the unnecessary inclusion of letters that change the meaning of the word, it can be used globally and internationally, and it is easily remembered because of its acceptability. This has been welcomed by other specialties.[3]

The letters may be employed in independent words or in words contained in a large statement. An example of the latter is the memorable description of Dowling–Degos disease by Wilson-Jones and Grice:[4] *d*emonstrating *d*usky *d*appled *d*isfigurements and *d*ark *d*ot *d*epressions, and *d*isclosing *d*igitate *d*owngrowths *d*elving *d*ermally.

Here, we list some of the "mono-letter" mnemonics that can be used as an aid in teaching dermatology: "a" in Addison's disease [asthenia, areola pigmentation, arterial hypotension, alimentary abnormality (anorexia, symptoms of acute abdomen), anxiety, axillary and pubic hair thinning]; "d" and "m" in pellagra [dementia, diarrhea, dermatitis, death, meats (mostly fats), molasses, meal (corn)]; "l" in a dermatopathology pattern with superficial and deep perivascular infiltrates with lymphocytes predominant [light eruption (polymorphus), lupus erythematosus, lymphocytic infiltrate of Jessner + deep figurate/gyrate erythema, Lyme disease, lues (syphilis) (+ plasma cells), lymphoma, leukemia, leprosy, indeterminate type (+ histiocytes)]; "p" in telogen effluvium (pregnancy, protein depletion, pills, propranolol, pyrexia, parturition, psychic stress); "p" in lichen planus (purple, polygonal, planar or flat, papules, pruritic, persistent, penile); "s" in superficial chronic glossitis [smoking, spirit (alcohol), spices, syphilis, sharp objects (trauma), sepsis (chronic debilitating diseases)].

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Aggressive squamous cell carcinoma developing in a giant epidermal cyst of the abdomen

Epidermal cysts (ECs) are common benign skin tumors. The development of malignant tumors within ECs is rare. We report a case of aggressive squamous cell carcinoma (SCC) developing in a giant EC of the abdomen.

A 48-year-old Japanese woman was referred to our clinic with a gradually enlarging, painful tumor on the right lower abdominal area, which had been incised and biopsied at the previous hospital 20 days earlier. The biopsy specimen demonstrated poorly differentiated atypical keratinocytes, suggesting the development of SCC. She had noticed the tumor for more than a decade; however, it had enlarged rapidly during the previous 6 months. Physical examination revealed a 7.6 × 4.1-cm cystic nodule on the right lower abdominal area (Fig. 1a,b). White keratinous material and pus were drained

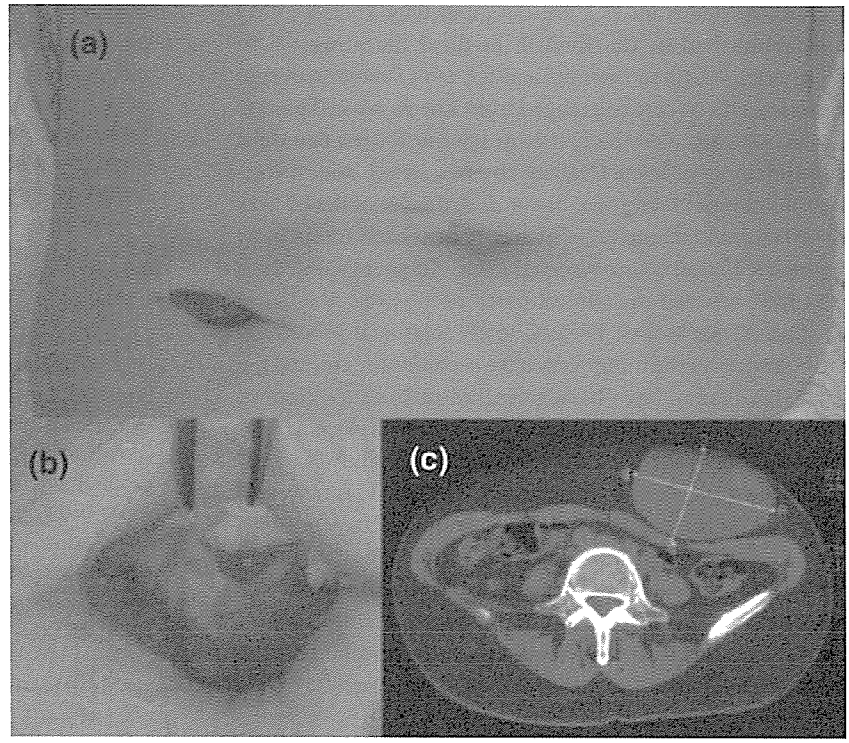

Figure 1 (a,b) Physical examination revealed a cystic nodule on the right lower abdominal area. (c) Computed tomography scan, performed at the previous hospital, showed a 9.3 cm × 6.6 cm cystic tumor. No invasion of the rectus abdominis muscle was suspected

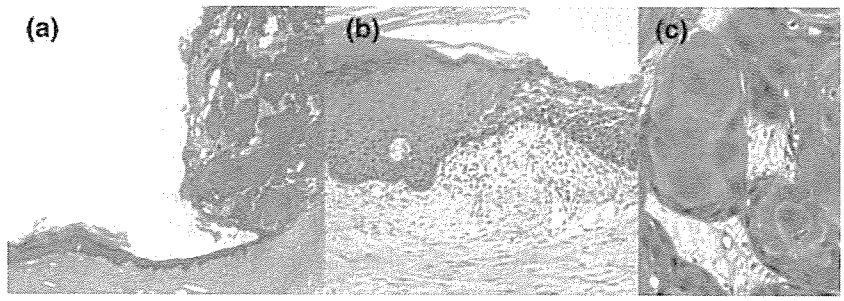

Figure 2 (a) Histologic observation of the nodule removed from the abdominal area revealed a tumor composed of normal cyst walls with a continuum to exophytic proliferation of atypical cells (hematoxylin and eosin stain, ×100). (b) Cyst wall composed of benign squamous epithelium with transition to squamous cell carcinoma (hematoxylin and eosin stain, ×200). (c) Atypical cells with distinct intercellular bridges and keratinized towards the center of the nest to form a cancer pearl (hematoxylin and eosin stain, ×400)

from the surgical scar. Computed tomography (CT) scan, performed at the previous hospital, showed a 9.2 × 6.6-cm huge cystic tumor, just above the abdominal fascia (Fig. 1c). For both diagnostic and therapeutic purposes, the tumor was excised with a 2-cm margin including the anterior layer of the rectus abdominis sheath. Microscopic examination of the surgical samples revealed exophytic proliferation of poorly differentiated squamous cells developing from the cyst wall (Fig. 2a), which was composed of benign squamous epithelium showing epidermal keratinization (Fig. 2b). In high-power view, poorly differentiated polygonal pleomorphic squamous cells with hyperchromatic nuclei were shown invading the dermis (Fig. 2c). Multiple atypical mitosis was also observed. Although the surgical margin was free of cancer cells, and the systemic CT scan and gallium scintigraphy demonstrated no metastasis at the time of surgical excision, the patient experienced cough and dyspnea 4 months after the excision. Chest CT and transbronchial lung biopsy revealed lung metastasis of SCC. Systemic chemotherapy with 1000 mg of 5-fluorouracil (5-FU) for 5 days and 100 mg of cisplatin for 1 day was initiated; however, the metastatic lesions spread rapidly, and the patient died as a result of respiratory failure 10 months after the operation. The subsequent autopsy confirmed multiple metastasis of SCC to the kidney, liver, mesentery, peritoneum, and skin.

SCCs arising from ECs are rare, and only 10 cases have been published in the English medical literature.[1–10] In these cases, ECs had been present for 2–132 months (mean, 34 months). The cyst size ranged from 1 to 10 cm in diameter (mean, 4.8 cm), and rapidly enlarged during the last 6 months in the majority of cases. Of these 10 cases, lymph node metastasis developed in only one. In our case, the size of the EC was large (10 cm in diameter), which may be related to the most aggressive clinical course reported so far. Another factor which may have affected the clinical outcome was that the lesion was incised for biopsy. Because of the incisional procedure, the boundary of the tumor may have become obscure, and the cancer cells may have been scattered to the surrounding tissue. In this case, both the large size and stimulation as a result of the incision may have led to the unfavorable clinical course.

Although the development of SCC within EC is relatively rare, the rapid enlargement of long-standing EC may be a sign of SCC development. In such cases, adequate and complete excision of the tumor is recommended to rule out the occurrence of SCC. Further systemic evaluation and careful follow-up of the patient are indicated because of the possibility of the rapid systemic metastasis, as observed in our case.

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Itraconazole in the treatment of cutaneous leishmaniasis

Dear Sir,

We read with great interest the paper by Dr Consigli *et al.*[1] reporting on the successful treatment of two cases of cutaneous leishmaniasis (CL) with itraconazole.[1]

There are other reports which support the results of Dr Consigli *et al.* with oral administration of itraconazole in the treatment of CL, which were not referenced in the aforementioned article, but when considering the hierarchy of evidence for therapeutic studies it is generally accepted that randomized, controlled, clinical trials (RCTs) provide more reliable evidence than case reports.[2–4] It is for this reason that the emphasis of this letter is on the RCTs concerning efficacy of oral itraconazole in the treatment of CL.

Dr Consigli *et al.* referred to four RCTs to support their results, including two studies from India, one article from Kuwait and one from Iran.[5–8]

We wish to mention some points regarding the RCTs that Dr Consigli *et al.* used to support their results. Dr Consigli *et al.* referenced a paper by Momeni *et al.*[8] to support the efficacy of itraconazole in the treatment of CL. It should be considered that Momeni *et al.* mentioned at the conclusion of their paper that "the low response rate in patients receiving itraconazole indicates that itraconazole cannot be used as the single agent in the treatment of patients with CL caused by *L. major*".[8]

Dogra *et al.*, in two small sample RCTs of 20 and 24 patients with CL, compared the results of treatment with oral itraconazole with no treatment, or placebo, for 6 weeks in an endemic area for *L. tropica* and concluded that oral itraconzole had promising antileishmanial potential.[5,6] In another small size RCT in Kuwait, involving a total of 24 cases with CL, the authors concluded that itraconazole appeared to be a suitable antileishmanial drug with minor side-effects in comparison with those reported with pentavalent anitimoniate.[7]

We also wish to refer to a more recently published double-blind, placebo-controlled RCT on 200 patients in an endemic area for CL, owing to *L. major*, in which the efficacy of an 8-week course of oral itraconazole at a dose of 200 mg/day was not significantly different from the placebo: 59% vs. 53%, respectively.[9]

All the above-mentioned reports evaluated treatment with itraconazole in Old World CL. Although we could not find any appropriately designed RCTs concerning itraconazole in

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LETTER TO THE EDITOR

Animation as a useful tool for assessing functional status in psoriatic arthritis

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy of unknown etiology that is closely associated with psoriasis. The severity of joint inflammation has often been underestimated in patients with PsA; in fact, erosive and deforming arthritis occurs in 40%—60% of these patients [1], which may result in significant functional impairment as well as joint destruction. Because functional impairment markedly reduces the patient's

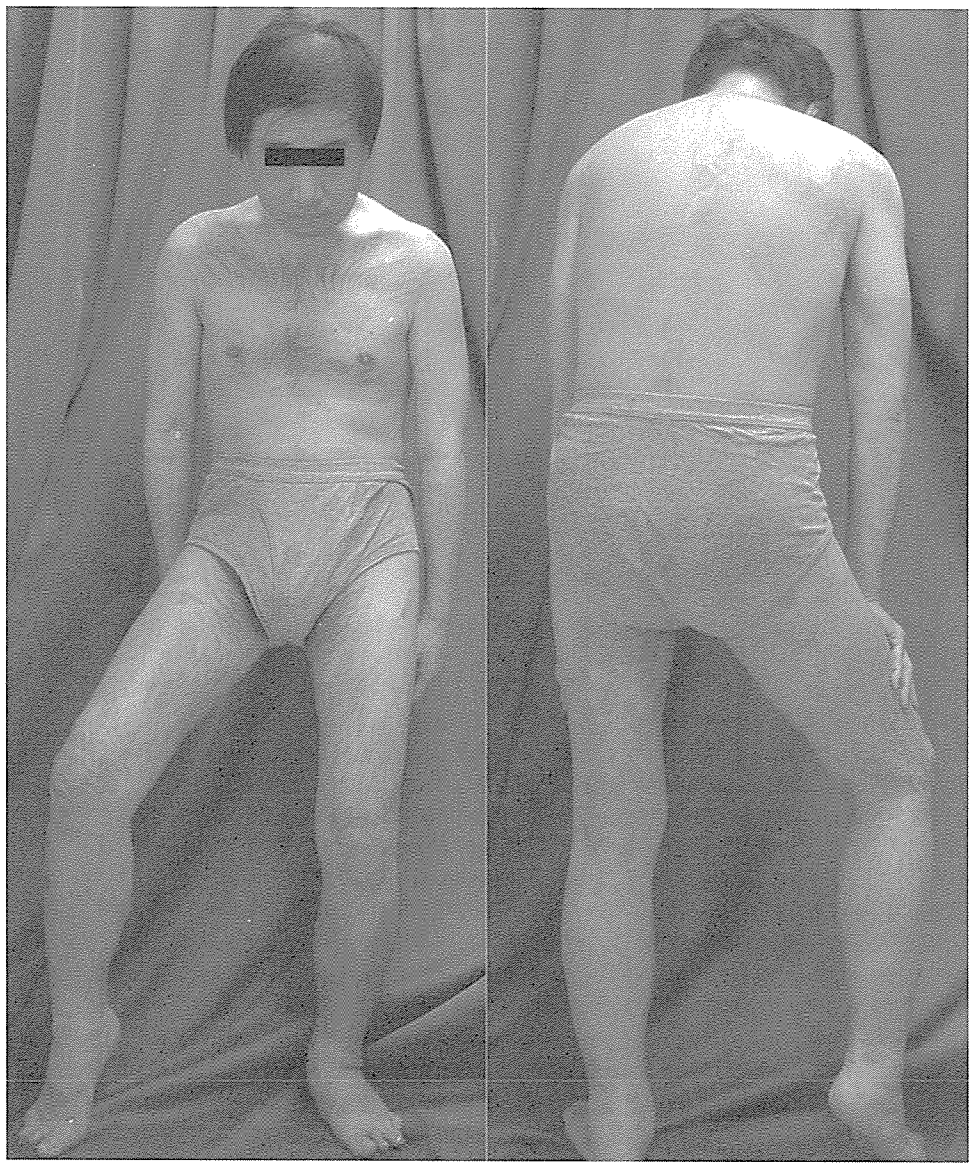

Fig. 1 Skin showing erythroderma and apparent multiple joint deformations.

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quality of life (QOL), an accurate assessment of the patient's functional status is important. However, to date, the appropriateness of measures to assess disease activity in PsA has not been confirmed [2]. This study presents a case of severe PsA successfully treated with infliximab and effectively assessed using animation.

A 39-year-old Japanese male presented with a 10-year history of psoriasis and a 3-year history of arthritis. He had no other significant past history. At the initial examination, his skin presented with erythroderma (Fig. 1), and he was suffering from severe pain in the axial and acral joints. ^{99m}Tc bone scintigraphy showed increased uptake in the shoulder joints, spine, hip joints, knee joints, and left ankle joint (Fig. 2). He had difficulty in everyday movement, even in picking up a pen (supplemental data 1). Given the increasing pain, and deformity and functional impairment of the affected joints, we initiated therapy with the monoclonal anti-TNF-α antibody infliximab 3 mg kg^{-1}, infused at weeks 0, 3, and 6, and the pain was effectively alleviated from the day after the first treatment. Dramatic functional recovery was obtained immediately after the third treatment (supplemental data 2). At week 6, the patient reached the American College of Rheumatology response criteria for improvement (ACR 70), criteria that were originally designed for the clinical evaluation of rheumatoid arthritis. Such a response requires a 70% reduction in the

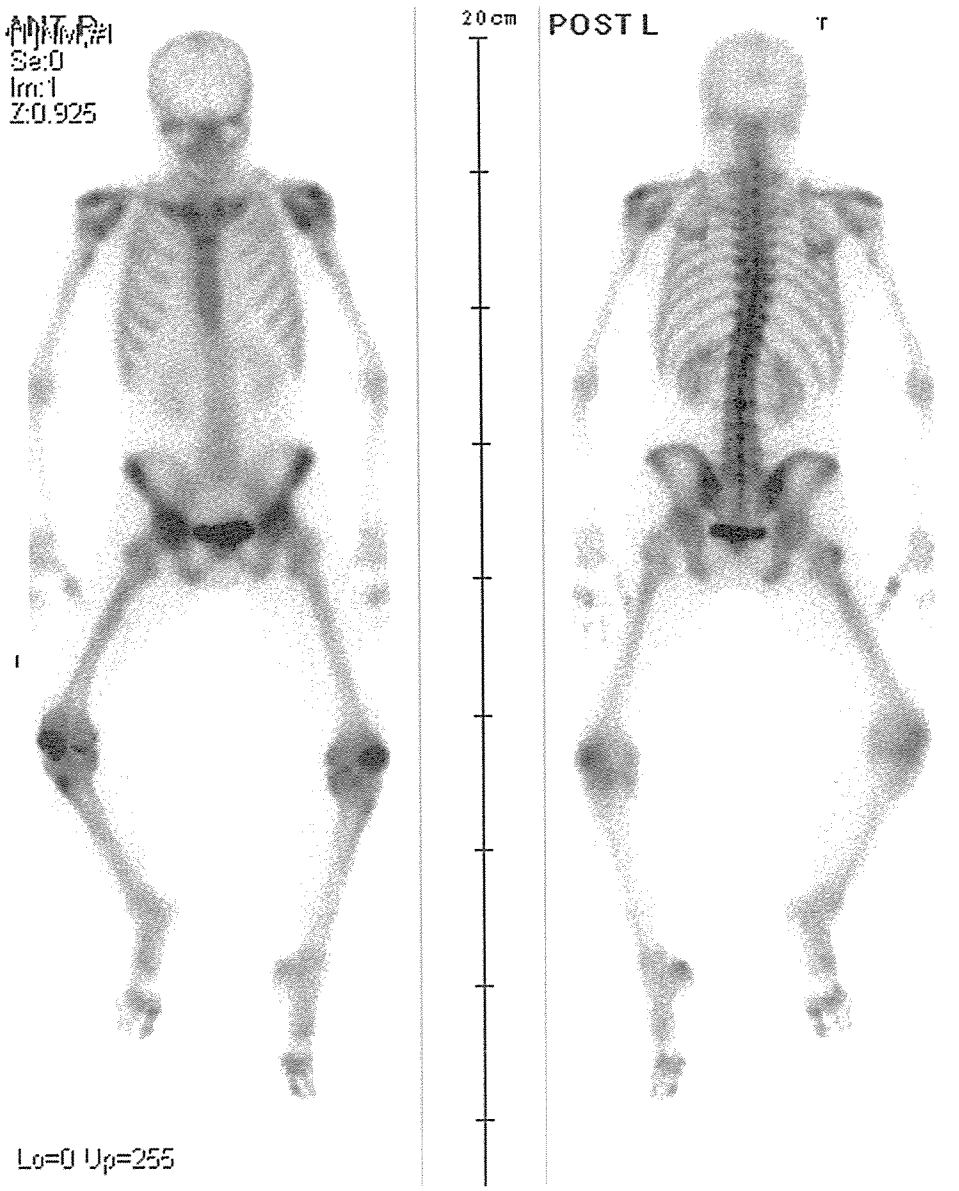

Fig. 2 ^{99m}Tc bone scintigraphy demonstrates increased uptake in the shoulder joints, spine, hip joints, knee joints, and left ankle joint.

number of swollen and tender joints, and a reduction of 70% in three of five parameters: physician global assessment of disease, patient global assessment of disease, patient assessment of pain, C-reactive protein or erythrocyte sedimentation rate, and degree of disability in Health Assessment Questionnaire score. The skin also showed significant improvement, paralleled by a decline in the psoriasis area and severity index score from 25.7 at week 0 to 2.7 at week 6.

PsA sometimes manifests a severe debilitating erosive arthropathy and the course of this disorder is progressive from within the first year of diagnosis [1]. Early diagnosis and therapy based on an accurate assessment of functional status are important to prevent joint deformity and functional impairment.

Conventional ways of assessing functional status in PsA include the Health Assessment Questionnaire (HAQ), Medical Outcomes Study Short-Form 36 (SF-36), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and Bath Ankylosing Spondylitis Functional Index (BASFI) [2]. However, each is based on a questionnaire, which makes them subjective. For greater objectivity, we used animation as an assessment tool in this case. We were able to assess this patient's movements objectively by observing how long it took to move and how smoothly movements were made. Before infliximab therapy it took him 12 s to pick up a pen, whereas after that therapy it took him only 4 s, and those movements were smooth and painless. We propose animation as a tool for assessing functional status in PsA.

Early, aggressive therapy is important to improve symptoms and QOL, and to reduce the disability associated with PsA [3]. Recently, tumor necrosis factor alpha inhibitors, including infliximab, etanercept, and adalimumab, have been used for PsA, and they have shown great efficacy in placebo-controlled double-blind trials [4–6]. Infliximab was highly effective in this case. However, because infliximab has not been approved as a treatment for PsA in Japan, this is the first case report of this therapy on a Japanese patient.

In conclusion, animation should be considered as a useful tool for assessing functional status in PsA.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jdermsci.2006.09.010.

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Effective Esophageal Balloon Dilation for Esophageal Stenosis in Recessive Dystrophic Epidermolysis Bullosa

Abstract

Recessive dystrophic epidermolysis bullosa (RDEB) is an inherited disorder of squamous epithelium that results in dystrophic scarring of the skin after minor trauma. RDEB is classified into two subtypes: Hallopeau-Siemens (HS) and non-Hallopeau-Siemens (nHS). Although severe scarring of the skin is the most common and obvious complication of the disease, esophageal scarring with formation of long strictures may also develop. Treatment options for esophageal stenosis in patients with RDEB include steroids, hyperalimentation, esophageal dilation and replacement. This report describes a child who was dilated immediately after diagnosis of severe esophageal stenosis subsequent to nHS-RDEB and managed successfully. Endoscopic esophageal balloon dilation under fluoroscopic control was very useful for detecting the region of stenosis and bougienage. The literature on such injuries is reviewed here, and the problems associated with the treatment of children with esophageal stenosis associated with RDEB are discussed.

Key words
Non-Hallopeau-Siemens recessive dystrophic epidermolysis bullosa · esophageal stenosis · endoscopic esophageal balloon dilation · dysphagia

Résumé

L'épidermolyse bulleuse dystrophique récessive (RDEB) est un désordre de l'épithélium qui entraîne l'apparition de cicatrices dystrophiques de la peau après des traumatismes mineurs. La RDEB est classifiée en deux sous-types: Hallopeau-Siemens (HS) et nonHallopeau-Siemens (nHS). Quoique les cicatrices cutanées soient la complication la plus habituelle, une des complications particulières de cette maladie est la formation de cicatrices oesophagiennes avec des sténoses. Les options thérapeutiques pour la sténose oesophagienne chez les patients avec l'EBDR sont les corticoïdes, l'hyperalimentation, les dilatations oesophagiennes ou le remplacement oesophagien. Ce rapport décrit le cas d'un enfant qui a été dilaté immédiatement aprés le diagnostic de sténose oesophagienne sévère associé à un nHS-EBDR et traité avec succès. La dilatation oesophagienne endoscopique par ballon sous contrôle radioscopique est très utile pour détecter les limites de la sténose et faire la dilatation. La littérature sur de telles lésions est revue, et les problèmes associés avec le traitement des enfants qui présentent une sténose oesophagienne associée à une RDEB sont discutés.

Mots-clés
Epidermolyse récessive nonHallopeau-Siemens

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Resumen

La epidermolisis bullosa distrófica recesiva (RDEB) es un trastorno heredado del epitelio escamoso que conduce a la cicatriz distrófica de la piel ante traumas menores. La RDEB se clasifica en dos subtipos la Hallopeau-Siemens (HS) y la no Hallopeau-Siemens (nHS). Aunque las retracciones de la piel son las complicaciones más comunes de la enfermedad, puede producirse también estenosis esofágica. Las opciones de tratamiento para ésta son esteroides, alimentación parenteral, dilatación esofágica y sustitución. Este trabajo describe un niño que fue dilatado inmediatmente tras el diagnóstico de estenosis esofágica severa en una nHS-EDDR y que fue tratada con éxito. La dilatación endoscópica con balón bajo control fluoroscópico fue muy útil para detectar la región de la estenosis y la dilatación. Revisamos la literatura sobre tales lesiones y discutimos los problemas asociados a ellas.

Palabras clave
Epidermolisis bullosa · estenosis esofágica

Zusammenfassung

Die dystrophe Epidermolysis bullosa (RDEB) ist eine rezessive Erkrankung des Plattenepithels, die nach Minimaltraumen zu dystrophen Narben führt. Die RDEB wird in zwei Untergruppen unterteilt: die Hallopeau-Siemens-Form (HS) und die Nicht-Hallopeau-Siemens-Form (nHS). Obwohl schwere Narbenbildung der Haut die häufigste und unausweichliche Komplikation dieser Erkrankung ist, können sich auch langstreckige Ösophagusstenosen entwickeln. Ihre Behandlung umfasst sowohl die Gabe von Steroiden, eine hyperkalorische Ernährung, Ösophagusbougierungen als auch Ösophagusersatzoperationen. Hier wird ein Kind mit einer schweren Ösophagusstenose bei nHB-RDEB vorgestellt, das erfolgreich bougiert werden konnte. Die endoskopische Ballondilatation des Ösophagus unter fluoroskopischer Kontrolle war sehr hilfreich, um die Stenose zu lokalisieren. Die Literatur zu solch schwierigen Fällen wird vorgestellt und die Behandlung von Kindern mit RDEB und Ösophagusstenose diskutiert.

Schlüsselwörter
Rezessive dystrophe Epidermolysis bullosa · Ösophagusstenose · Behandlung

Introduction

Epidermolysis bullosa (EB) is a group of inherited skin diseases that primarily affects the skin and mucous membranes, resulting in blisters and erosions after even relatively minor mechanical trauma. Recessive dystrophic EB (RDEB) is one of the severest subtypes of EB caused by a mutation in *COL7A1*, which encodes type VII collagen, a major component of the anchoring fibrils [3,7,11]. RDEB is classified into two subtypes: Hallopeau-Siemens (HS) and non-Hallopeau-Siemens (nHS) [3]. Immunohistochemical analysis using an antitype VII collagen monoclonal antibody demonstrates a complete absence of staining in the skin of persons with HS-RDEB, while staining is only severely to moderately reduced in nHS-RDEB [11].

Esophageal problems develop insidiously and are caused by bulla formation, ulceration, and edema, and ultimately lead to formation of strictures that may in turn cause complete esophageal obstruction with regurgitation of blood-stained secretions [6,8]. RDEB is responsible for esophageal lesions consisting of webs or stenosis [8]. Esophageal stenosis of RDEB is treated by various methods, such as steroids, esophageal balloon dilatation [2] or replacement procedures [1,5].

Feurle et al. recommended avoidance of tangential shearing forces induced by bougienage and endoscopy, and instead recommended the use of inflatable dilator balloons which produce a vertical pressure that seems to be less harmful [2]. However, we present here our successful experience with a 9-year-old boy with nHS-RDEB complicated with esophageal stenosis, who required endoscopic esophageal balloon dilation. The literature on this type of treatment is reviewed here, and the problems associated with the treatment of children with esophageal stenosis of RDEB are discussed.

Case Report

A male infant weighing 2860 g was delivered vaginally after 41 weeks of gestation. He was diagnosed to have nHS-RDEB at 6 months of age and was managed conservatively. Details of the clinical, immunohistochemical and molecular study of this patient have been described previously [11]. Release of flexion contractures of the bilateral fingers was performed at the age of 5 years. At the age of 7 years, he had the first occurrence of dysphagia. He suddenly became unable to swallow liquids or food at the age of 9 years and was admitted to our institute.

Ulcers, hemorrhages and erosions formed on his skin, fingers, axilla, anus, knees and feet. The patient was unable to swallow even saliva. At the time, his height was 140 cm and his weight was 26 kg. Laboratory examinations revealed iron-deficiency anemia, including a hemoglobin level of 9.9 g/dl, hematocrit of 30.5% and serum iron of 18 µg/dl. No other abnormal findings were found such as carcinoembryonic antigen as a tumor marker.

A barium esophagogram showed a 7-cm long, string-like annular stricture in the upper one-third of the esophagus near the pyriform recessus (Fig. **1 a**). Based on the finding of severe esophageal stenosis, it was planned to perform endoscopic esopahageal dilatation under general anesthesia using a laryngeal mask. The tip of the endoscope was generously lubricated with a gel containing steroids for prophylaxis. Esophagoscopy showed an edematous tight stricture beginning from the esophageal orifice (Fig. **1 b**). Under fluoroscopic control, a Rigiflex™ balloon dilator catheter (Boston Scientific MICROVASIVE™, Boston Scientific Corporation, Michigan, MJ, USA) lubricated with a gel containing steroids was placed at the lower end of the stenosis, which had been localized previously by radiography. First, the balloon with an outer diameter of 0.6 cm was insufflated with saline for 30

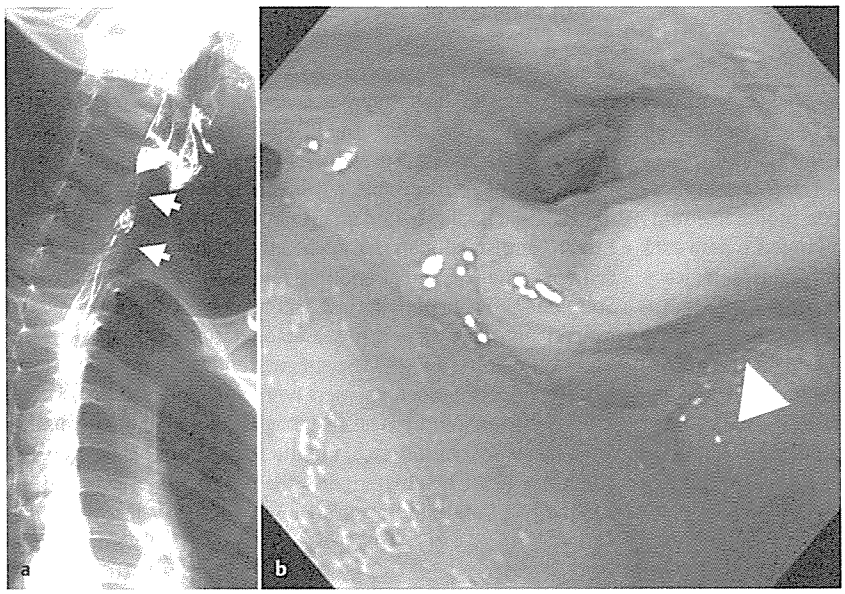

Fig. **1 a** and **b** **a** A barium esophagogram at the age of 7 years after occurrence of dysphagia showed a 7-cm long, string-like annular stricture in the upper one-third of the esophagus near the pyriform recessus (white arrow). **b** Esophagoscopy showed an edematous tight stricture beginning at the esophageal orifice (white arrowhead).

seconds without difficulty and the insufflated pressure was then released (Fig. **2 a**). The same maneuver was then performed for one minute. Thereafter, the balloon with an outer diameter of 1.0 cm was sufficiently insufflated successively for 30 seconds and then for 1 minute (Fig. **2 b**). At removal, the esophagogram showed the release of stenosis and no leakage of enhancing medium from the esophagus.

An esophagogram obtained the next day revealed slight esophageal stenosis and good passage of enhancing medium. Dysphagia ceased immediately and the patient was drinking and eating a soft, semisolid diet 1 day after the procedure. He has not had clinical dysphagia 5 years after esophageal dilation and has required no further dilations. A barium-swallow X-ray taken recently shows slight stenosis of the upper esophagus.

Subsequently, he developed two skin lesions of squamous cell carcinoma at 12 years of age and the entire lesions were excised in the department of dermatology of our institute [7].

Discussion

RDEB is one of the hereditary bullous disorders affecting both the skin and the esophagus [2]. To our knowledge, there is no data comparing HS-RDEB and nHS-RDEB regarding the incidence of esophageal stenosis. We have therefore elected to discuss RDEB without differentiating between HS-RDEB and nHS-RDEB.

In patients with RDEB, minor trauma is followed by blistering and scarring [3]. Therapy for RDEB consists of skin care, supportive care for other organ systems, and the use of systemic therapies in an attempt to alter disease progression [1]. These include severe scarring of the skin with acquired syndactyly and joint contractures [5]. In 20% of patients, mucosal surfaces are affected, and esophageal scarring with long strictures may develop, resulting in severe dysphagia [10]. Some agents, such as steroids, tetracycline, and phenytoin, have been used in the past for systemic therapy, but none of them has proven beneficial [1]. In the esophagus, recurring blistering and vulnerability eventually lead to strictures or complete obstruction [2]. However, control

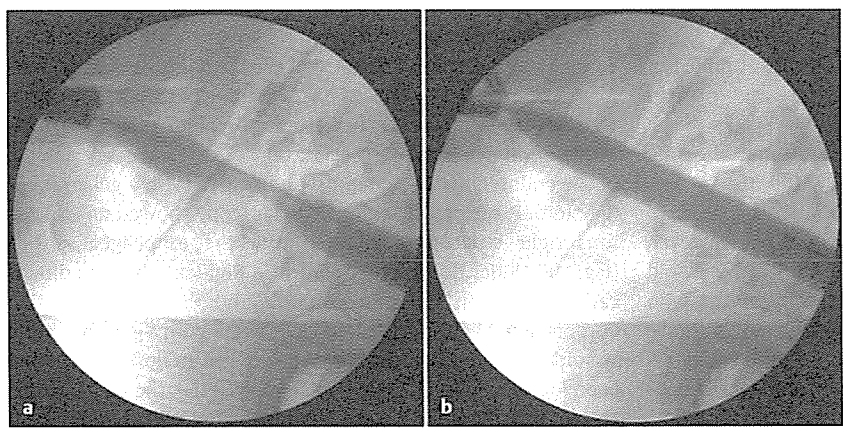

Fig. **2 a** and **b** **a** Under fluoroscopic control, a Rigiflex™ balloon with an outer diameter of 0.6 cm was insufflated with saline for 30 seconds without difficulty. **b** Thereafter, the balloon with an outer diameter of 1.0 cm was insufflated successively for 30 seconds and then for 1 minute.

of esophageal traumatization is difficult, and strictures and stenosis develop gradually because they are only noticed by the patients at a late stage [2]. The pattern of esophageal involvement may consist of ulceration leading to multiple areas of narrowing or of a smooth, tapered, stenotic segment, usually 2–6 cm in length [6]. Any segment of the esophagus may be involved, although the most common sites are the cervical and distal portions [6]: lesions occur most commonly in the cervical (50%) followed by the distal portion (25%) [8].

Dysphagia in patients with epidermolysis bullosa who have esophageal involvement commonly begins in childhood, although presentation in an adult is not rare [6]. Some investigators advise medical therapy in the early stage of esophageal stenosis and point out that the response of the patient to this therapy is more dramatic than the change in radiological appearance [2,8]. Because dysphagia due to severe esophageal stenosis was prominent and urgent in our patient, endoscopic esophageal balloon dilation was considered as the first treatment. It was necessary to use a balloon dilator introduced via a guide wire to keep the region of the stricture open. Some investigators have advocated the use of gastrostomy feeding or parenteral hyperalimentaion to ameliorate the poor nutritional status of RDEB patients [1]. Gastrostomy also makes nasogastric tube placement unnecessary, avoiding discomfort to the patient and the potential of hazardous effects on the proximal anastomosis [1].

It is reported that all forms of bougienage, for example, the Eder-Puestow instrument or the Molony bougie as well as endoscopy, should be avoided because they cause tangential shearing forces, rather than vertical pressure, leading to a detachment of skin and mucous membranes with eventual scarring or stricture formation [2,10]. In addition, the trauma of endoscopy may result in esophageal bulla, ulcers and hemorrhage [10]. On the other hand, esophageal dilations are recommended for cervical lesions or webs but carry the risk of perforation in cases of extensive strictures [4]. It has also been reported that dilations are beneficial mostly in adults with inactive disease rather than in children with active disease, and are a temporary rather than a permanent cure, with worsening of the strictures after 1 or 5 years of follow-up after dilations [4]. Balloon dilation was selected in 9 of 11 children with bougienage for esophageal stenosis in Japan [9]. In 10 children, esophageal stenosis ceased after one bougienage, and in all 11 patients, esophageal stenosis was improved by these dilation methods. Therefore, we considered that esophageal balloon dilation under fluoroscopic control should be recommended as a first-line therapy for children with RDEB with moderate or severe esophageal stenosis.

In the case described here, successful management implied the need for minimal contact with the skin and the mucous membranes, which means that application of a tracheal tube needed to be avoided, ECG electrodes were fixed in place with steroid paste and the face mask was not placed directly in contact with the patient's face. No serious complications were observed during or after endoscopic esophageal balloon dilation. Kern et al. [8] reported that esophageal perforation occurred in one of 23 esophageal dilations in 7 patients with RDEB. Even though we have not been able to conduct a controlled study of this rare disorder, our experience, nevertheless, may be useful for the management of such patients.

As another form of treatment, an esophageal replacement procedure may be considered for extensive esophageal stricture [1,5,12]. Demiroğullari et al. [1] reported on esophageal replacement surgery in 10 RDEB patients with esophageal stenosis since 1969. During the postoperative course, 4 of 9 (44%) had various anastomotic problems. Although different types of procedures and conduits have been described for esophageal replacements for conditions other than RDEB, the most commonly used form in childhood is a colonic procedure for RDEB patients, with 8 colon replacements in 9 cases [1]. Alternatively, Touloukian et al. [12] suggest an ileocolonic interposition to create an anastomosis with a suitable diameter, preventing gastric reflex, and are of the opinion that gastrostomy should be avoided because of the risk of gastrocutaneous fistula. On the other hand, Harmel [5] suggests that a reverse gastric tube has significant advantages over colon esophagoplasty because the procedure time is shorter and the procedure allows matching to the caliber of the native esophagus.

For medical therapies, it has been suggested that phenytoin should be administered to suppress the genetically altered dermal collagenase. However, there is no definitive proof of the effectiveness of phenytoin in the esophagus analogous to the findings in the skin [2]. Some reports claim that high doses of corticosteroids have stabilized both the symptoms and strictures in some patients [10].

In summary, the aim of our report is to demonstrate the effectiveness of endoscopic esophageal balloon dilation in the treatment of RDEB and to show that surgical intervention can be avoided in children. We feel that this procedure has an important role in the management of such children. Esophageal strictures can develop in patients with RDEB who require lifelong medical attention including continuous management of esophageal complications.

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LETTER TO THE EDITOR

Possible role of endoplasmic reticulum stress in the pathogenesis of Darier's disease

KEYWORDS
sarco/endoplasmic reticulum Ca^{2+} ATPase;
ATP2A2;
Chaperone;
Keratinocytes

Darier's disease (DD, keratosis follicularis; OMIM 124200) is an autosomal dominant genodermatosis characterized by persistent, greasy, scaly papules which show abnormalities in keratinocyte adhesion and differentiation including acantholysis, suprabasal clefting, and unusual dyskeratosis. Mutations within the *ATP2A2* gene encoding the sarco/endoplasmic reticulum Ca^{2+} ATPase type 2 (SERCA2) are found in DD patients, indicating that SERCA2 plays an important role in keratinocyte adhesion and differentiation [1]. However, the precise mechanisms underlying the histological hallmarks in DD have not yet been fully elucidated.

The endoplasmic reticulum (ER) may serve specialized functions including the post-translational modification, folding, and assembly of newly synthesized secretory proteins. Various conditions can interfere or disrupt ER function, and these are collectively grouped into ER stress-associated diseases. ER stress provokes an ER stress response, which includes upregulation of ER chaperones, inhibition of gene translation, degradation of the misfolding proteins, and induction of a transcription factor C/EBP homology protein (CHOP) that leads to cell apoptosis [2].

SERCA2 actively transports Ca^{2+} from the cytosol back into the ER lumen to maintain the correct Ca^{2+} concentration in the ER. ER stress can be induced by a decrease in Ca^{2+} concentration within the ER. These suggest that SERCA2 abnormalities in DD are caused by the low Ca^{2+} in the ER lumen, resulting in ER stress. This study was designed to address a hypothesis that ER stress is involved in formation of the characteristic histological features of DD.

The lesional skin specimens and cultured keratinocytes obtained from a 17-year-old female with DD were used for study. Diagnosis of DD was determined by dermatologists based upon clinical and histopathological features (the mutation C318R in *ATP2A2* was previous reported [3]). The normal human keratinocytes and skin specimens were obtained from a normal adult female. In order to observe the ER stress response in keratinocytes, we examined the expression of calreticulin [4], BiP/GRP78 [5] and CHOP/gadd153 [6]. The primary keratinocyte cultures were grown in serum-free keratinocyte growth medium (KGM, Clonetics) and then treated with the stressors, 1.0 μM thapsigargin [7] or 1.0 mM *S*-nitro-*N*-acetyl-DL-penicillamine (SNAP) [8] for 48 h.

The specimens were embedded in OCT compound, and 10 μm thick sections were cut. The treated keratinocytes and cryosections were stained with rabbit polyclonal antibodies against calreticulin (Stressgen), rabbit polyclonal antibodies against or CHOP/GADD153 (Santa Cruz) or goat polyclonal antibodies against BiP/GRP78 (Stressgen), followed by treatment with FITC-conjugated secondary antibodies. To semiquantify the keratinocytes expression of calreticulin, CHOP/GADD153 and BiP/GRP78, respectively), we measured fluorescence intensity of each cell using the digital photograph (Gel Plotting Macros; NIH Image; provided in the public domain by the National Institutes of Health, Bethesda, MD, and available at http://rsb.info.nih.gov/nih-image/). We graded the fluorescence intensity of stained cells as follows: Level 1: poor staining; Level 2: moderate fluorescence levels; Level 3: bright cytoplasmic fluorescence. Typical staining pattern of each Lever was shown in Fig. 1A. Intensity value was estimated from; (the number of level 1 cells × 1) + (the number of level 2 cells × 2) + (the number of level 3 cells × 3)/the total number of the cells, and repeated the same experiment four times. Finally, the expression ratio

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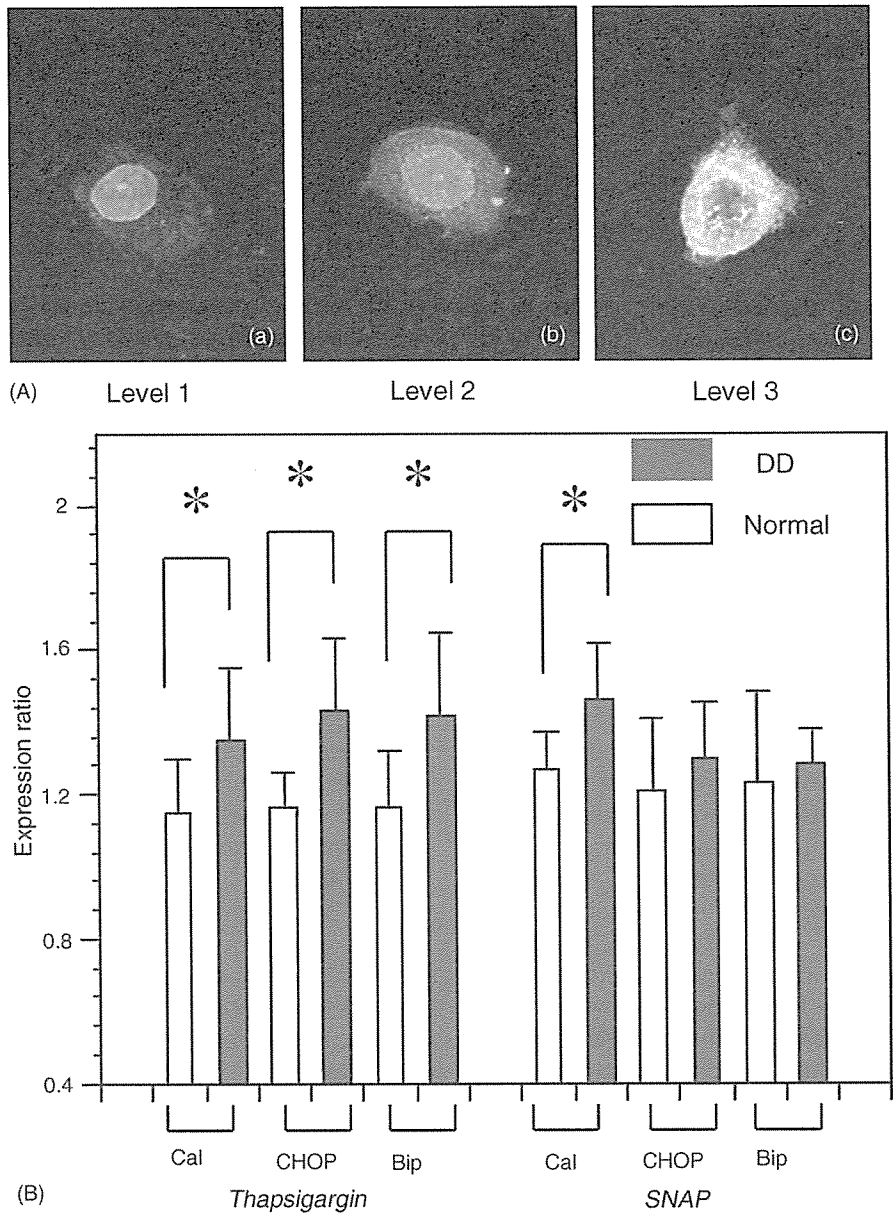

Fig. 1 Expression of calreticulin, CHOP/GADD153 and BiP/GRP78. DD (■) and normal (□) keratinocytes were treated with thapsigargin and SNAP for 48 h, and expression of calreticulin (Cal) CHOP/GADD153 (CHOP) and BiP/GRP78 (Bip) was scored and quantified as intensity value. (A) We counted to a hundred of the cells in a chamber, and classified as follows; Level 1: dark and poor staining in the cytoplasm (a); Level 2: moderate green deposit in the cytoplasm (b); Level 3: very bright cytoplasm with yellow colored (c). (B) DD keratinocytes induced expression of calreticulin, CHOP/GADD153 and BiP/GRP78 more than normal keratinocytes. Expression ratio was represented as the ratio of intensity values of stimulated to unstimulated cell samples. The results were plotted as a mean ± S.D. *Significant differences between DD and normal samples ($p < 0.02$).

was represented as the ratio of intensity values of stimulated to unstimulated samples.

The results of the culture cell study are shown in Fig. 1B. The expression of three molecules in DD keratinocytes was all higher than that in normal keratinocytes. Significant differences ($p < 0.02$) were found in thapsigargin-induced calreticulin, CHOP/GADD153 and BiP/GRP78 samples and SNAP-induced calreticulin sample.

Next, we examined the expression of calreticulin, CHOP/GADD153 and BiP/GRP78 in DD lesional skin. Hematoxylin and eosin sections clearly showed the dyskeratotic cells and corps ronds with the suprabasal cell layers. These cells stained with anti-calreticulin antibody (Fig. 2). We however failed to find immunostaining in any of the anti-Bip/GRP78 and CHOP/GADD153 in sections (data not shown). Skin section from normal control

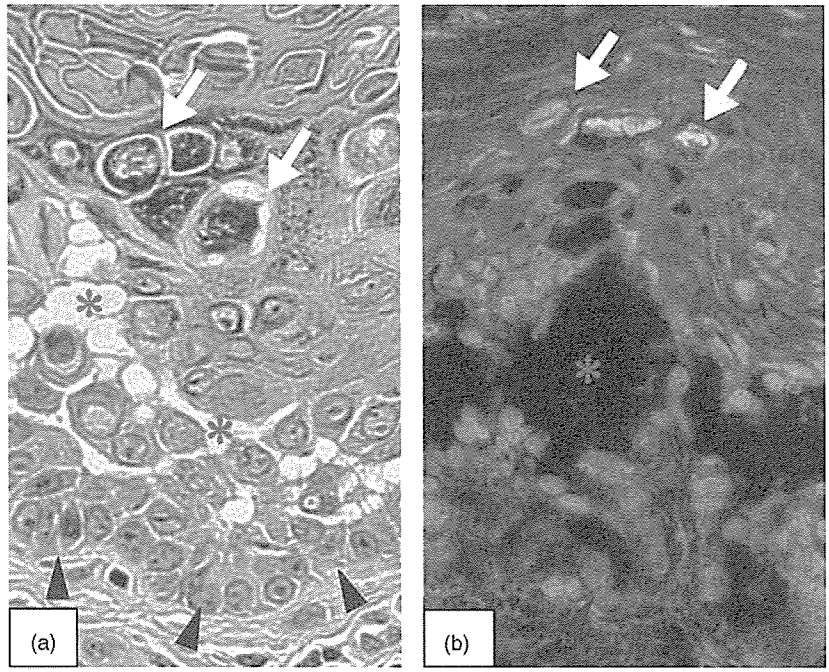

Fig. 2 Immunohistochemical analysis of DD skin. (a) Dyskeratotic cells, corps ronds (arrows), suprabasal clefts (*) and acantholytic keratinocytes were observed (H&E staining). (b) Expression of calreticulin was detected in dyskeratotic cells (arrows). Blue arrowheads indicate the position of the basement membrane.

showed no immunoreactivities for any of those molecules.

The ER stress response is a mechanism by which cells protect themselves against ER stress. One response involves the up-regulation of genes encoding ER chaperone proteins to increase protein folding activity and to prevent protein aggregation. When the functions of the ER are severely impaired, apoptosis is induced via the transcriptional induction of CHOP/gadd153. The ER stress inducers, thapsigargin and SNAP were added to the keratinocyte cultures because both the DD and normal keratinocytes without any stressors showed a relatively low level of expression of above three ER chaperons. Those stressors induced ER stress by different mechanisms. This study showed that the levels of ER chaperons calreticulin, CHOP/gadd153 and Bip/GRP78 were increased in DD keratinocytes compared with normal control keratinocytes, suggesting that ER stress might be somehow involved with pathogenesis of Darier's disease.

Hakuno reported that the dissociation of intra- and extracellular domains of desmosomal cadherin and E-cadherin are characteristics of acantholytic cells in DD [9], this phenomenon might be explained by ER stress leading to important protein misfolding or misassembly. In addition, we found strong expression of calreticulin in dyskeratotic cells in DD lesional skins. Although we observed little or no detectable expression of CHOP/gadd153 in these cells, such dyskeratotic cells might result from apoptosis induced by ER stress.

This study suggests that the ER stress may be involved in the pathogenesis of DD. The treatment of DD has mainly included oral retinoids, or topical retinoids for localized DD. Recently some agents are shown to have an inhibitory effect on ER stress in the other organs [10], so we suggest that drugs which control ER stress in keratinocytes might hold significant potential for the treatment of DD.

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Chain Saw Blade Granuloma: Reaction to a Deeply Embedded Metal Fragment

We report a case of foreign body granuloma caused by a metal fragment from a chain saw. Since our patient had no history of injury and since several incisional biopsy specimens showed no foreign body, we had difficulty arriving at the diagnosis. Finally, pantomography revealed a small piece of metal and x-ray microanalysis of this piece was consistent with the edge of a chain saw. To our knowledge, this is the first case reported of foreign body granuloma caused by a chain saw blade fragment.

Report of a Case. A 72-year-old Japanese man presented with a 6-month history of a nontender, hard, subcutaneous nodule on his lower jaw (**Figure 1** A). A biopsy specimen of the nodule demonstrated granulomatous inflammation throughout the dermis with collagen fiber degeneration (Figure 1B). We initially suspected infectious granuloma, such as cutaneous tuberculosis, a deep fungal infection, or a malignant tumor. However, cultures for mycobacteria, fungi, and bacteria all yielded negative results and findings from polymerase chain reaction analysis were also negative for *Mycobacterium tuberculosis*. Pantomography, performed to rule out a dental fistula, revealed a foreign body in the lower jaw (**Figure 2**A). A piece of metal at a depth of about 7 mm was removed (Figure 2B). The piece was a 4.0×3.5-mm, sharp-edged shard of metal (Figure 2C). By x-ray microanalysis, it was found to be composed of tungsten, cobalt, argent, zinc, cadmium, and copper. We questioned the patient in detail whether he had had any exposure to metallic materials. His occupational history indicated that he had been a forestry worker and he used to operate chain saws. The piece of metal was consistent with the edge of a chain saw. Taken together, the metal fragment found from his lower jaw might have become inadvertently implanted in the skin during his work. The small piece of metal subsequently produced a large subcutaneous granulomatous allergic reaction.

Comment. Cobalt and zinc are among the metals capable of inducing granulomatous reactions.[1,2] The metal from ear piercing and eyebrow tattooing can produce allergic contact granuloma.[3,4] Although we could not precisely confirm which agent induced the granuloma in our patient, we suggest that the cause could be one of the metals that can induce allergic contact granuloma. This case presented several diagnostic difficulties because of the absence of a history of specific injury causing implantation of the metal. Other cases of metal implantation without a history of injury include graphite,[5] a broken piece of mower blade, and a wire stabbing. Therefore, foreign body granulomas should be included in the differential diagnoses of any granulomatous skin lesion even if there is no history of metal implantation. We recommend ra-

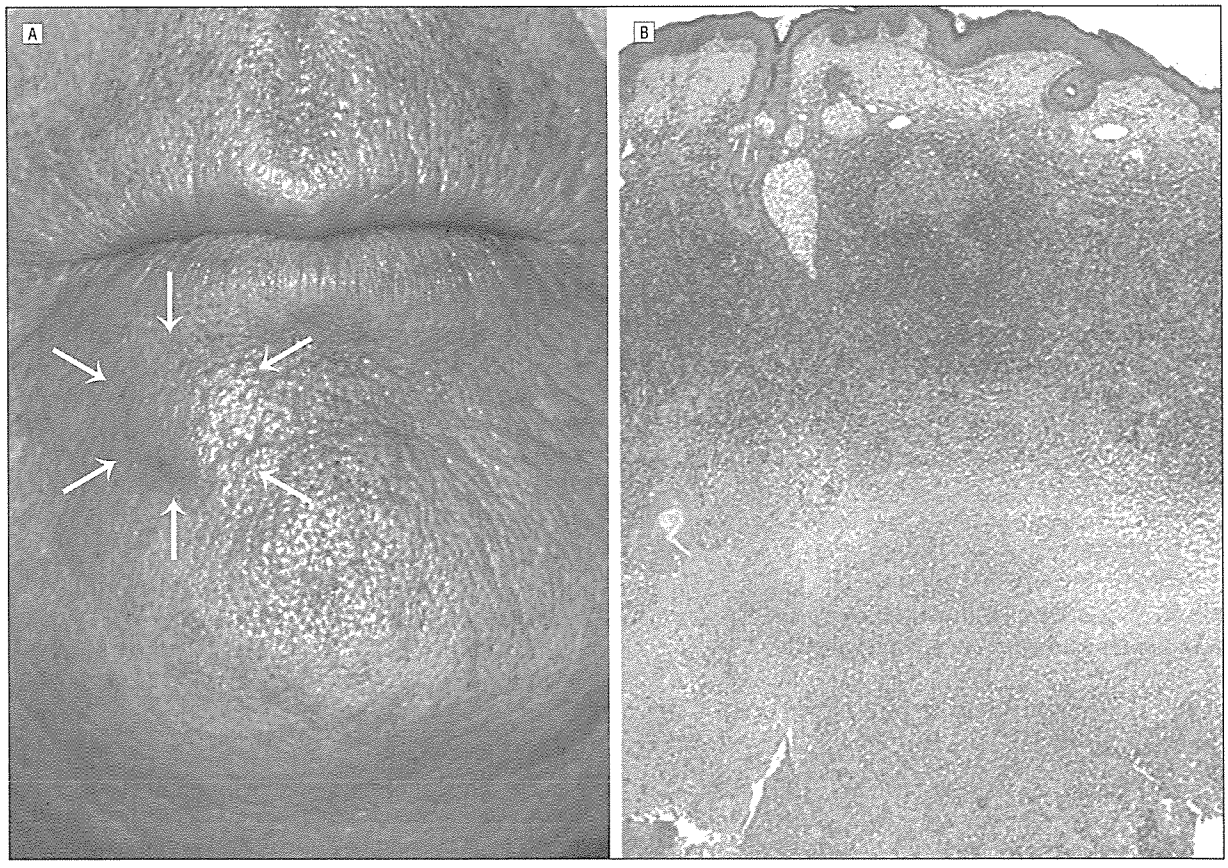

Figure 1. Clinical and histopathologic findings. A, A nontender, 2.5×2.0-cm, dark-reddish subcutaneous hard nodule on the lower jaw. B, Histopathologic examination showed granulomatous inflammation throughout the dermis with collagen fiber degeneration (hematoxylin-eosin, original magnification ×4).

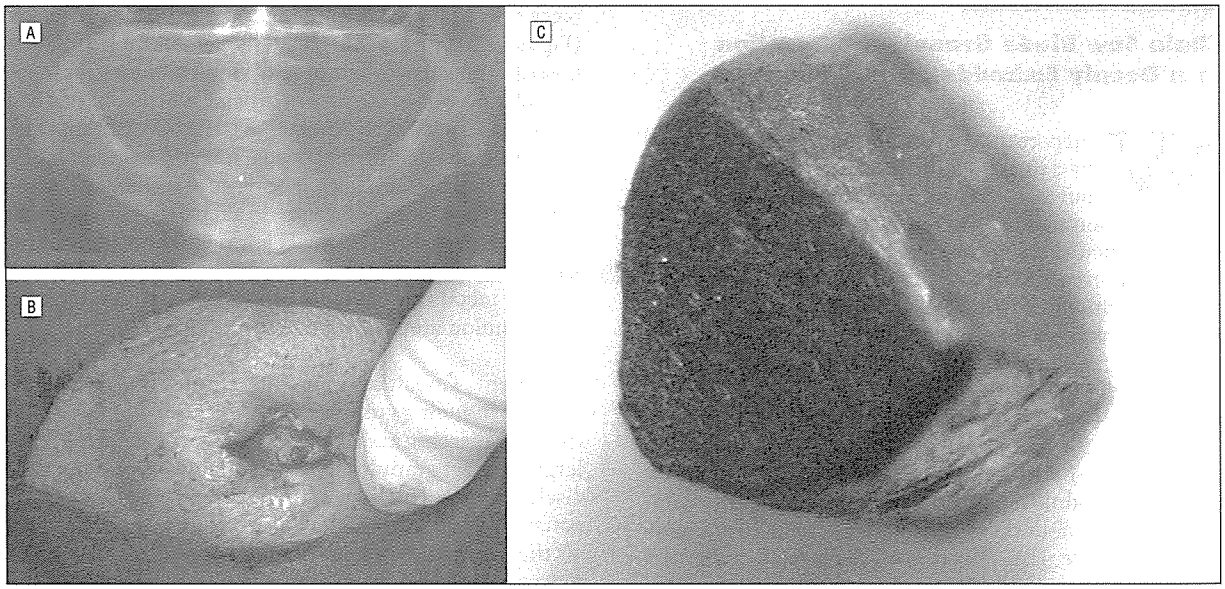

Figure 2. A, Pantomography revealed an electron-dense foreign body in the soft tissue of the patient's lower jaw. B, A piece of metal was seen within the lower dermis at a depth of about 7 mm. C, A 4.0×3.5-mm-diameter sharp-edged shard of metal (high-power view, orginal magnification ×10).

diographic imaging when a superficial biopsy specimen fails to show evidence of a deeply implanted foreign body.

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Acute Generalized Exanthematous Pustulosis Induced by Clindamycin

Acute generalized exanthematous pustulosis (AGEP) involves numerous nonfollicular sterile pustular lesions associated with fever above 38°C, neutrophilic leukocytosis, an intensely pruritic rash, and in later stages, desquamation.[1] A high proportion of cases are triggered by drugs, especially macrolides and aminopenicillins. We report the first case, to our knowledge, of AGEP associated with the use of clindamycin in a black woman who was also undergoing therapy for systemic lupus erythematosus (SLE).

Report of a Case. A 38-year old black woman with a history of SLE, hypertension, diabetes mellitus, and depression presented with a 9-day history of an increasingly widespread, painful, and pruritic eruption composed of erythematous macules and papules, which occurred 4 days after starting oral clindamycin hydrochloride therapy (300 mg, 3 times a day) for a suspected intravenous site infection during a hospital admission for SLE-related pleuritis (**Figure 1**). Her medications included prednisone, methotrexate, fluoxetine, valacyclovir hydrochloride, alendronate sodium, atenolol, losartan potassium, hydroxychloroquine sulfate, clonidine, amlodipine besylate, furosemide, and insulin. She denied the use of alcohol or any herbal or over-the-counter medications. The erythematous plaques were studded with flaccid 1- to 2-mm pustules and involved more than 80% of her body surface area. Lesions evolved to broad areas of desquamation. Target erythematous lesions favored the extensors and were not mucosal. A discrete grouping of pustules was noted in the buccal mucosa, posterior hard palate, and subungually. Palmar erythema on the thenar and hypothenar eminences was also present. There was no scalp scaling, nail pitting, or other stigmata of psoriasis.

Therapy with clindamycin was discontinued a few days after the eruption began. She denied exposure to any new drugs for several years and never had pustular or psoriatic lesions.

She had a white blood cell count of $22.6 \times 10^3/\mu L$, with 99% neutrophils. Findings from blood and urine cultures, taken both prior to the initiation of clindamycin therapy and during this admission, were negative. Histopathological examination revealed numerous neutrophils, eosinophils, and subcorneal pustules, supporting a diagnosis of AGEP (**Figure 2**).

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A unique monoclonal antibody 29A stains the cytoplasm of amniotic epithelia and cutaneous basement membrane

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Summary

Background: The basic function of epithelia is to provide a boundary between tissue and its external environment, and is achieved by a wide variety of components including extracellular molecules. Multiple monoclonal antibodies raised against epithelial antigens have helped identify a range of distinct, novel protein epitopes.
Object: In this study, we raised a monoclonal antibody to detect a novel epithelial molecular component.
Methods: We have produced a mouse monoclonal antibody using normal human amniotic tissue as an immunogen. The monoclonal antibody was subsequently immunohistochemically screened, and the target antigen was cloned using an immunoscreening method.
Result: In the course of the screening, we identified unique antibody staining patterns within the cytoplasm of a subset of amniotic cells at intervals within the normal placental epithelia. By immunoscreening, we identified this candidate gene as

Abbreviations: BM, basement membrane; FITC, fluorescein isothiocyanate; IF, immunofluorescence; LR, laminin receptor; PBS, phosphate buffered saline; TBS, tris-buffered saline; TRITC, tetramethylrhodamine isothiocyanate

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laminin receptor (LR). By dot blot analysis, this antibody reacted with recombinant LR. The same localization of the antigen and LR was proved by a double staining immunofluorescence test in the placenta. This monoclonal antibody unexpectedly demonstrated linear staining within the dermal–epidermal junction of normal human skin but failed to react within the keratinocyte cytoplasm.

Conclusion: We have produced and characterized a novel monoclonal antibody 29A that recognizes an LR-related molecule, which demonstrated a unique staining pattern. This monoclonal antibody might be a useful tool for further investigations into the epithelial tissues and the cutaneous basement membrane (BM).

1. Introduction

The evolution of novel developmental mechanisms in epithelia allows animals to live in diverse ecological environments. This enables epithelia to have many functions as a protective barrier, play roles in the immune or endocrine systems. A wide variety of molecules participate in this maintenance and protection of epithelia. Many organs including the placenta and skin are thought to be related and possess similar epithelial structures, and it is known that organs can share multiple common molecules. Advances in immunology and molecular biologic methods have enabled the production of novel monoclonal antibodies and allowed us to clone the associated genes using these antibodies. Previous studies have identified several novel BM proteins which are expressed in both the placenta and skin [1–3].

The basement membrane (BM) of many epithelia is a highly specialized extracellular matrix that serves many functions, of which the most obvious is the attachment of the epithelia to underlying mesenchyme. It also influences such tissue behavior such as the growth, migration, and differentiation [4,5] of nearby cells. Moreover, degradation of this matrix is associated with tumor cell invasion and cancer progression [6]. Previous studies have showed that extracellular proteins such as type IV collagen, laminins, fibronectin, nidogen, and heparin sulfate proteoglycans appear to be BM components including skin and placenta BM [1–3,7,8].

Novel as yet unidentified molecules which play a crucial role in normal and abnormal conditions are though to be expressed in the epithelial and cutaneous BMs, and identification of such molecules may lead to significant progress in epithelial biology and furthermore in dermatological research. In this report, we have produced a monoclonal antibody using normal human amniotic epithelia as an immunogen. Interestingly, the resulting unique monoclonal antibody 29A stained the cytoplasm of amniotic epithelial in the placenta but was restricted to the basement membrane zone of the skin.

2. Materials and methods

2.1. Monoclonal antibody production

A monoclonal antibody was produced against normal human placental amnion using a technique previously described with some modifications [9]. Amnion was separated from the underlying connective tissue, and cut using scissors. Ten grams of the tissue was homogenized with a Polytron (Kinematica AG) in 20 ml of 40 mM phosphate buffer (pH 7.3) containing 150 mM NaCl and protease inhibitors, 1 mM *p*-amidinophenyl methanesulfonyl fluoride hydrochloride (Wako Pure Chemicals), 10 μg/ml leupeptin and pepstatin (Peptide Institute Inc.). After centrifugation at 10,000 × *g* for 20 min, the supernatant was again centrifuged at 100,000 × *g* for 60 min. The whole process was performed at 4 °C. The precipitate was suspended in 1 ml of the above buffer and immediately used for mouse immunization, and the rest stored as stock at −80 °C for further immunizations.

A BALB/c mouse was injected subcutaneously with 100 μg protein after mixing with adjuvant (TiterMax Gold, Cytrx Corp.) once a week for 3 weeks. On the third day after the last intraperitoneal immunization with 100 μg protein in buffer, spleen cells of the immunized mouse were fused with X63Ag8.653 mouse myeloma cells, using 50% polyethylene glycol 1500 (BDH Chemicals). The fused cells were cultured in RPMI 1640 medium (Invitrogen) supplemented with 15% fetal calf serum and 10% BM-condimed H1 (Boehringer) including HAT (Flow Co.) in 96-well plates. An indirect immunofluorescence (IF) method using frozen sections of normal human placental amnion was used for screening the supernatants from the growing cells. Every 3 weeks, the hybrid cell line of interest was cloned twice and injected to mice intraperitoneally previously treated with pristane (2,6,10,14-tetramethylpentadecane, Tokyo Kasei Co.).