Prurigo pigmentosa is a type of inflammatory dermatosis characterized by symmetrical pruritic erythematous papules that normally resolve with reticular pigmentation. In severe cases, edematous infiltrative plaques may be found, but usually no vesicles or bullae. We presented a 32-year-old Taiwanese female, a case of insulin dependent diabetes mellitus with sudden onset of vesicobullae upon erythematous papuloplaques over the face, neck and upper trunk, preceding an episode of diabetic ketoacidosis. Histopathology of the skin lesion revealed an intraepidermal bulla filled with neutrophils, atrophic epidermis, exocytosis, perivascular mononuclear cells and neutrophils infiltration involving dermis and hair follicles. The vesicobullae subsided after control of ketoacidosis by subcutaneous insulin injection. Our final diagnosis was bullous prurigo pigmentosa. Doxycycline was then added to complete the treatment and it was found to be effective in resolving erythema and post-inflammatory hyperpigmentation. Bullous prurigo pigmentosa is a rarely documented entity, we herein report a case and review the literature. (Dermatol Sinica 27: 103-110, 2009)

Key words: Bullae, Diabetes mellitus, Ketosis, Prurigo pigmentosa, Vesicles

INTRODUCTION

Prurigo pigmentosa is a rare inflammatory cutaneous disease of unknown etiology described first by Nagashima et al. in 1971. It is observed rather frequently in Japan, where more than 200 patients have been reported, but only a few cases have come to notice in other countries. In Taiwan, seven cases have been documented. It usually affected young people. Clinically, the rash occurs mainly on the central back, scapular, chest, clavicular and nuchal regions. It is characterized by recurrent, symmetrical, pruritic, erythematous papules which usually resolve while leaving gross reticular hyperpigmentation. In severe cases, however, they may also form edematous infiltrative plaques, but the presentation predominantly with vesicles or bullae is usually not the rule. Histologically, perivascular neutrophil infiltration, spongiosis, intraepidermal vesiculation, lichenoid infiltration with vacuolar degeneration of basal layer, and melanin incontinence all correspond well to the different stages of prurigo pigmentosa. Hence, prurigo pigmentosa is generally considered as a dermatosis.
diagnosed with clinical presentation and pathological consistency.

The term “bullous prurigo pigmentosa” was first introduced in 1998. Since then, only five cases have been reported as bullous or vesicular prurigo pigmentosa. We herein present a case of bullous prurigo pigmentosa associated with newly diagnosed insulin-dependent diabetes mellitus complicated with diabetic ketoacidosis and review the literature.

**CASE REPORT**

This 32-year-old woman came to our Emergency Department due to shortness of breath and vomiting for two days. We were consulted for the concomitant itching and tingling skin lesions over the scalp, forehead (Fig. 1A), chin (Fig. 1B), V-region of chest (Fig. 1C), and back (Fig. 1D) progressing over two weeks. In the beginning, pruritic erythematous polygonal macules were noticed over back in a symmetrical funnel-like pattern. Rapid progression with involvement of scalp, forehead, chin, post-auricular area, neck, and V-region of chest was noted three days before visiting our Emergency Department. These erythematous, edematous plaques were accompanied with aggravated itchy sensation, prominent focal confluence and infiltration especially over chest and back. Numerous crops of vesicles and tense bullae were also formed upon plaques (Fig. 1E, 1F). Reviewing her past history, she denied having any systemic illness. However, she had taken plum essence for two months, and Gentian (a kind of Chinese herb medicine) in recent two weeks. She denied applying any topical agents, such as medication, cosmetic lotions or creams, chlorhexidine disinfectant, or perfumes over areas of skin eruption. She admitted traveling three days prior to the eruptions without extensive sun exposure. Owing to the photosensitive distribution of acute eczema-like skin lesions, lupus erythematosus and photodermatitis were suspected initially, with other bullous dermatosis and erythema multiforme to be ruled out. Skin biopsy with direct immunofluorescence study was done over one bulla at anterior chest wall.

Aside from skin eruptions, our patient had polyuria, polydipsia, foamy urine, and five-kilogram weight loss in recent two months. She also suffered from postural dizziness. Laboratory examinations done at...
emergency room revealed: WBC 27,300 / μl, segment 88%, blood glucose 448 mg/dl, blood ketone 2+, urine ketone 3+, arterial blood gas analysis PH 7.24, HCO$_3$- 9.8. Diabetic ketoacidosis was impressed and she was admitted for further care.

During admission, her HbA1C was 12.5%(4.6-6.2), and C-peptide showed <0.3 ng/ml (0.9-4.0). Hypoinsulinism with chronic hyperglycemia was impressed, arriving at a final diagnosis of insulin-dependent diabetes mellitus. All autoimmune profiles such as antinuclear antibody (ANA), complements C3 and C4, rheumatoid factor (RF), anti-basement membrane antibody, and anti-intercellular substance antibody were normal. Pancreatitis markers such as amylase and lipase were also within normal limits. She was given adequate hydration for diabetic ketoacidosis and subcutaneous insulin injection to control her elevated blood sugar. Antihistamine and topical betamethasone-gentamicin cream were prescribed for pruritus control.

One week after correcting her blood sugar status, all vesicles and bullae resolved. Meanwhile, the erythematous edematous plaques (Fig. 2A, 2B) turned to brown patches in a net-like pattern (Fig. 2C, 2D). Pathology of acute stage lesion revealed an intra-epidermal bulla containing many neutrophils, atrophic epidermis, exocytosis, and perivascular mononuclear cells with neutrophils in dermis and hair follicles (Fig. 3). Immunofluorescence study showed negative findings. Taking together the emergence of symmetrical reticular-patterned brownish patches from infiltrated itchy erythematous plaques with bullae formation and the presence of diabetic ketoacidosis, we came to the final diagnosis of bullous prurigo pigmentosa.

She was then discharged with regular subcutaneous insulin injection, antihistamine, topical steroid cream, and doxycycline 100
mg twice a day. On follow up, decrease of residual erythema and post-inflamatory hyperpigmentation was noted two weeks (Fig. 2E, 2F) and four weeks (Fig. 2G, 2H) later. We have kept doxycycline for two months and no relapse was noted for at least 10 months after discontinuation of doxycycline under the strict blood sugar control.

DISCUSSION

We presented a case of bullous prurigo pigmentosa with multiple itching bullous and vesicular eruptions superimposed on symmetrical, pruritic, eryhematous papules over neck, chest, back (which are typical locations of prurigo pigmentosa), as well as scalp, forehead, chin, and post-auricular region (which are not typical locations of prurigo pigmentosa). ‘Bullous prurigo pigmentosa’ was used to highlight this severe form of rarely mentioned entity. Although the histopathological findings of an intraepidermal bulla filled with neutrophils is seldom seen in the typical presentation of prurigo pigmentosa, we believed this a consequence of neutrophil exocytosis, spongiosis, ballooning degeneration, leading to bullae formation. It is interesting to find out that the occurrence of vesicles coincides with the acute onset of ketosis and leukocytosis, which may be the cause of this severe form of distinct dermatosis.

Vesicles were mentioned in the clinical presentation of 11 cases of prurigo pigmentosa from 1971 to 1997.7 The term ‘bullous prurigo pigmentosa’ was first used in 1998, presented as numerous vesicles and bulla on the back and anterior chest throughout the whole clinical course of the disease.6 A total of 6 cases termed bullous or vesicular prurigo pigmentosa were documented in the English literature (Table 1).6-11 These 6 cases, 4 male and 2 female, aged 17 to 32, all had lesions over shoulders and back. Only one of them involved forehead. Although 4 of them did not have a history of concomitant ketonemia, the 2 cases with ketouria noted association of vesicles two weeks before the diagnosis of diabetes mellitus.6,11 Our case shared similar clinical characteristics with these cases. For examples, all cases were young patients who had intense pruritic bullous or vesicular formation asides from eryhematous papules symmetrically distributed over typical locations (back, chest), as well as good response to tetracycline antibiotics. However, our case showed facial involvement which may indicate its higher severity both clinically and pathologically. Moreover, our case is associated with insulin-dependent diabetes mellitus complicated with diabetic ketoacidosis, which had been implicated in
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**Table. I Comparison of Bullous/Vesicular Prurigo Pigmentosa in Our Study with the Literature**

<table>
<thead>
<tr>
<th>Age, sex</th>
<th>Race</th>
<th>Onset</th>
<th>Location</th>
<th>Association</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murao et al. (1996)</td>
<td>30, M</td>
<td>Japanese</td>
<td>Acute</td>
<td>Chest, back -&gt; abdomen, legs, forehead</td>
<td>Hyperglycemia, Ketouria (On diet)</td>
</tr>
<tr>
<td>Kubota et al. (1998)</td>
<td>32, M</td>
<td>Japanese</td>
<td>Acute</td>
<td>Chest, back -&gt; neck</td>
<td>NIDDM Ketouria</td>
</tr>
<tr>
<td>Matsumoto et al. (2001)</td>
<td>21, M</td>
<td>Japanese</td>
<td>Chronic</td>
<td>Upper back, shoulders</td>
<td>Nil</td>
</tr>
<tr>
<td>Requena et al. (2005)</td>
<td>13, F</td>
<td>Caucasian</td>
<td>Chronic relapsing</td>
<td>Upper back, nape, intermammary skin, shoulders</td>
<td>Nil</td>
</tr>
<tr>
<td>De Francesco et al. (2006)</td>
<td>17, M</td>
<td>Caucasian</td>
<td>Chronic relapsing</td>
<td>Lower back, right axilla, right chest, right flank</td>
<td>Nil</td>
</tr>
<tr>
<td>Kim et al. (2007)</td>
<td>23, F</td>
<td>Korean</td>
<td>Acute</td>
<td>Chest, back</td>
<td>Nil</td>
</tr>
<tr>
<td>Our case report (2009)</td>
<td>32, F</td>
<td>Taiwanese</td>
<td>Acute</td>
<td>Back -&gt; face, scalp, neck, chest</td>
<td>IDDMM, DKA</td>
</tr>
</tbody>
</table>


Prurigo pigmentosa, but not bullous prurigo pigmentosa. Furthermore, our patient showed clinical responsiveness to insulin and doxycycline, a tetracycline antibiotic similar to minocycline used successfully in all previous cases.

The cause of prurigo pigmentosa has yet to be determined. Many factors have been implicated in the pathogenesis of prurigo pigmentosa. Sunlight, sweating, friction, contact allergens, weight loss (by fasting, dieting, anorexia nervosa), insulin-dependent diabetes mellitus and ketosis have been reported in some cases of prurigo pigmentosa, but none of them showed consistent association. Of these, ketosis is the most acceptable factor because it is commonly observed in association with fasting, dieting and insulin-dependent diabetes mellitus. Ketosis can generate oxygen radicals and result in excess cellular oxidative stress in type 1 diabetic patients. Ketosis also increases the serum level of pro-inflammatory cytokines interleukin-6 (IL-6), interleukin-8 (IL-8), and MCP-1 (monocyte chemoattractant protein-1). Up-regulation of reactive oxygen species (ROS) and pro-inflammatory cytokines simultaneously in the cutaneous system may contribute to the formation of prurigo pigmentosa.

We have wondered if bullae formation represented more severe diabetic ketoacidosis. When we compare bullous and non-bullous type of prurigo pigmentosa, it is a pity that we cannot find out any predominant character in bullous prurigo pigmentosa. Both ketosis (including ours) and non-ketosis associated cases have been documented in bullous prurigo pigmentosa, same as described in the non-bullous type. All other characters such as gender, race, onset, location did not show any predominance.
in bullous prurigo pigmentosa. In this way, it seems that individual susceptibility to ROS may play a more important role in the differential expression between bullous and non-bullous type of prurigo pigmentosa. It would be interesting to find out if there is any difference in free radical scavenging system between bullous and non-bullous lesion of prurigo pigmentosa.

Although dapsone and sulfamethoxazole are effective for prurigo pigmentosa, minocycline appears to be the treatment of choice due to its higher safety profile. Dapsone and sulfonamide are thought to exert their anti-inflammatory effect by suppressing the generation of oxygen intermediates, thus protecting tissues from injury. Although the exact action of minocycline is not clear, the therapeutic effects include the inhibition of oxygen intermediates, neutrophil chemotaxis, and mitogenic response. All prurigo pigmentosa cases, with or without bullous formation, reported dramatic response to tetracycline group antibiotics (minocycline and doxycycline), with the inhibition of new vesicle formation in a few days. Besides its anti-inflammatory effect, tetracycline might also play a role in the regulation of melanogenesis. Keratinocyte-generated nitric oxide (NO) has been implicated in stimulating epidermal melanogenesis. Interestingly, tetracycline has long been shown to exert its inhibitory effect on nitric oxide synthases. Recently, doxycycline has been found to decrease NO production from inducible nitric oxide synthases (iNOS) by destabilization of iNOS mRNA via decreased expression of p38 MAPK. Therefore, it is reasonable to speculate that doxycycline might inhibit melanogenesis by decreasing NO production. The eventual decreased ROS loading also alleviates the inflammatory skin condition.

In summary, prurigo pigmentosa can be presented with bullous lesions. Bullous prurigo pigmentosa can easily be misdiagnosed as other bullous dermatosis such as bullous lupus erythematosus, photodermatitis with bullous formation, etc., especially when the initial erythematous plaques are not well-defined and the reticular pattern has not yet revealed. It should be considered in the differential diagnosis of pruritic papulovesicular lesions, especially when typical locations or clinical associated conditions are met. The bridging role of ROS between ketosis and prurigo pigmentosa skin, and between doxycycline and anti-inflammation and anti-melanogenesis have led us to speculate its possible key role in the pathomechanism of prurigo pigmentosa. Further studies in ROS susceptibility between bullous and non-bullous prurigo pigmentosa is warranted.

REFERENCES
水泡性色素癢疹
- 病例報告與文獻回顧

蔡坤穎1 邱健群1 許仲瑤1
台北長庚紀念醫院皮膚科1 桃園長庚大學醫學院1
嘉義長庚醫院皮膚科2

色素性癢疹是一種發炎性的皮膚病，它的特徴是在身上產生對稱性的紅色丘疹性癢疹，並在急性病灶消失後遺留下網狀色素斑。在比較嚴重的病例中可以看到較為浸潤的水腫斑塊，但一般不會看到水泡的產生。我們在此報告一位32歲胰島素依賴性糖尿病女性，在她的臉、頸、胸、背的紅色浸潤丘疹與斑塊上產生了許多嚴重的水泡，之後併發了糖尿病酮酸中毒。病理報告顯示在表皮層內的水泡充滿了嗜中性白血球的聚集、萎縮的表皮層、血球的趨外性，以及在真皮層血管周圍與毛囊周圍的淋巴球與嗜中性白血球浸潤。以皮下注射胰島素控制酮酸中毒後，皮膚水泡與丘疹斑塊也隨之緩解。我們將此病例診斷為水泡性色素癢疹。我們使用去氧羥四環素(doxycycline)來完成療程，並發現它對於退紅與發炎後色素沉著有幫助。水泡性色素癢疹是一個鮮為報告的皮膚疾病，我們在此報告一病例並回顧相關文獻。

（中華皮誌：27：103-110，2009）