Tegafur-Uracil 引起之類似紅斑性狼瘡的皮膚病灶
－病例報告－

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Lupus Erythematosus-
like Skin Lesions Induced by Tegafur-Uracil
-A Case Report-

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Tegafur-Uracil (UFUR) is a second generation anticancer agent. Few skin lesions are associated with UFUR therapy. Skin lesions with features of lupus erythematosus occurred in a 69-year-old man after starting UFUR treatment for 2 weeks for gastric adenocarcinoma. The diagnosis of drug-induced lupus erythematosus was supported by classic histopathologic findings of cutaneous lupus erythematosus, positive antinuclear (speckled and nucleolar pattern), and anti-SSA/Ro and SSB/La antibodies. The skin lesions resolved within 2 weeks after discontinuation of UFUR and treatment with steroids, but recurred on readministration of UFUR. This may be the first reported case of UFUR-induced lupus erythematosus-like skin lesions in Taiwan. UFUR should be considered as a possible cause of lupus erythematosus-like skin lesions during UFUR therapy. (Dermatol Sinica 22: 173-177, 2004)

Key words: UFUR, Lupus erythematosus-like skin lesions

UFUR 爲一種綜合了 uracil 和 tegafur 這兩種藥物的第2代抗癌藥。少數的皮膚疾病與接受 UFUR 的治療有關。本篇報告一例69歲罹患胃癌男性病患服用 UFUR 大約兩周時，出現類似紅斑性狼瘡的皮膚病灶。而根據發現有典型皮膚紅斑性狼瘡的組織病理特徵，以及有陽性反應的抗核抗體 (包括點狀和核仁型態)，以及抗 Ro 和抗 La 抗體，診斷為藥物所引發的紅斑性狼瘡。皮膚病灶停藥並接受類固醇治療後，約兩周內緩解。但再次給藥時又再度地復發。這 曲是台灣首例報告因服用 UFUR 引發類似紅斑性狼瘡的皮膚病灶。UFUR 應被列為在接受治療時，會引發類似紅斑性狼瘡病灶可能的原因。(中華皮誌 22: 173-177, 2004)
INTRODUCTION

Tegafur-uracil (UFUR) has become an important drug in the treatment of cancer. Tegafur [1-(2-tetrahydrofuryl)-5-fluorouracil] is a prodrug that is converted to 5-fluorouracil (5-FU) and has been reported to be less toxic with a higher therapeutic index. The additional advantage of tegafur is oral administration, an important consideration to improve the quality of life in these patients. Tegafur in combination with uracil is thought to have greater antitumor activity due to the inhibitory effect of uracil on the degradation of 5-FU by hepatic dihydropyrimidine dehydrogenase. A variety of cutaneous manifestations have been reported in patients treated with fluorouracil agents. Herein, we present a unique case that developed lupus erythematosus (LE)-like skin lesions while receiving UFUR.

CASE REPORT

A 69-year-old man had undergone a total gastrectomy with lymph node dissection for poorly differentiated gastric adenocarcinoma in April of 2003. Postoperatively, elevated CA-199 (859 U/ml) was noted. Chemotherapy with UFUR 1300 mg (tegafur 400 mg/day and uracil 900 mg/day) and etoposide 100 mg daily were initiated. Approximately two weeks later, he developed skin lesions on the face, shoulders and upper extremities, and was referred to our department for further evaluation and treatment.

He denied other systemic disease and history of drug allergy. Dermatological examination revealed numerous 2-5 mm well-demarcated, violaceous maculopapular lesions in a photodistribution involving the face (Fig. 1A), shoulders (Fig. 1B), and upper extremities. Some lesions were ulcerated or crusted. Violaceous maculopapules on the palms (Fig. 2A) and periungual erythema (Fig. 2B) were also noted. A skin biopsy from a shoulder lesion revealed atrophy of the epidermis with necrotic keratinocytes and prominent vacuolar alteration of the basal cells, and a lymphohistiocytic infiltration in the upper dermis (Fig. 3). Direct immuno-fluorescence (DIF) examination for IgG, IgA, IgM, C3 showed negative results. A presumptive diagnosis of LE was made.

Fig. 1
Patient with well-demarcated, violaceous maculopapules in a photodistribution on the face (A) and shoulders (B).

Fig. 2
Violaceous maculopapules on the palms (A) and periungual erythema (B) were noted.
Antinuclear antibody (ANA) titers were 1:320 and 1:40 in the speckled and nucleolar pattern, respectively. Anti-Ro and anti-La antibodies were also positive. Test for antihistone antibody was not available in our laboratory. The following data were negative: anti-Sm, anti-RNP, anti-Jo, anti-Scl 70, and anti-nDNA antibodies. Serum C3, C4 were within normal limits. Other laboratory data including complete blood cell counts revealed mild anemia and leukopenia.

Because skin lesions induced by etoposide is rare, UFUR was suspected to be the cause of LE-like skin lesions in our patient. UFUR was immediately stopped, and he was treated with systemic and topical steroids. The skin lesions resolved within 2 weeks. The patient was again given UFUR; about five days later the skin lesions recurred on the original sites, but resolved once again by discontinuation of UFUR and treatment with steroids. Later the follow-up of anti-nDNA antibody was negative, and serum C3, C4 were normal.

**DISCUSSION**

Our patient developed several features of drug-induced lupus erythematosus (DILE) while taking UFUR about 15 days. The skin lesions showed a photodistribution. The histologic features of the skin lesions were consistent with cutaneous LE. He had positive ANAs, anti-Ro and anti-La antibodies. The clinical and laboratory findings were consistent with DILE, which was further supported by the recurrence of LE-like skin lesions on readministration of UFUR. Yoshimasu et al. in 2001 described the first case of discoid LE (DLE)-like lesions induced by UFUR in an English language journal. In a Japanese language journal, the frequency of UFUR-induced skin lesions was about 1.77% among 29586 patients who received UFUR. The reported cutaneous manifestations induced by fluorouracil agents were as follows: acral erythema, acral hyperpigmentation, serpentine hyperpigmentation, photosensitivity, dermatomyositis, mucositis, Stevens-Johnson syndrome, Mucha-Habermann disease-like eruptions, seborrheic dermatitis, LE-like skin lesions and exacerbation of systemic LE (SLE). Another study of skin lesions induced by fluorouracil agents found DLE-like lesions in 10.3% of the patients. Among them, UFUR had the highest rate of DLE-like lesions (18%), followed by tegafur (9%) and fluorouracil (4%).
DILE is a well-known condition. DILE can be precipitated by cardiovascular, antimicrobial, anticonvulsant and antihypertensive agents. Patients with DILE generally present with clinical symptoms and laboratory findings consistent with a mild form of SLE while taking the drug. Criteria proposed for the diagnosis of DILE are as follows: (1) exposure to a drug suspected to induce DILE; (2) no history for SLE prior to the use of the drug therapy; (3) detection of positive ANAs with at least one clinical sign of SLE; (4) rapid improvement and gradual fall in the ANAs and other serologic findings upon withdrawal of the drug. The most common symptoms of DILE are fever, arthritis and serositis. Abnormal hematologic findings and central nervous system and renal involvement are rare. Cutaneous manifestations are uncommon features in DILE, ranging from 2 to 26% in hydralazine and procainamide-induced LE, in contrast to 71.5% of patients with SLE. However, the prevalence of skin manifestations in DILE varies according to the offending agents. For example, thiazide diuretics and calcium channel blockers often present with photosensitivity and subacute cutaneous LE-like skin lesions.

There is controversy concerning the period the implicated drug may provoke the onset of the signs of DILE. The duration of the implicated drug used before onset of DILE ranges from 3 weeks to 2 years, and symptoms and signs resolve in days to weeks and rarely in years. In several reports, the interval between initiation of fluorouracil agents and the onset of skin lesions varies from forty-eight hours to twenty days. For DLE-like lesions induced by fluorouracil agents, the mean duration of drug administration was about 8 months, and the mean regression time of lesions after the discontinuation of drugs was 35 days (7-60 days). In our patient, the duration before onset of LE-like skin lesions was about 15 days, and the skin lesions resolved within two weeks.

DIF examination had a negative result in our patient. It is known that specimens taken from sun-protected areas tend to give a negative result. In addition, positive lupus band test was reported only in about 41% of DLE-like skin eruptions induced by fluorouracil agents. ANAs are positive in 95% to 100% of patients with DILE; it often shows a homogenous pattern, and is mainly directed against histones or single stranded DNA. The findings of positive anti-histone and negative anti-nDNA antibodies and normal serum complement values are also characteristic for DILE. Bonsmann et al. described that anti-Ro and/or anti-La antibodies were found to be positive in the majority of drug-induced subacute LE. However, abnormal blood laboratory findings (anemia, leukopenia, thrombocytopenia) are unusual and rarely reported in DILE; but some patients have mild such symptoms. Our patient also developed mild anemia and leukopenia. The parameters used to make a diagnosis and distinction between DILE and idiopathic LE are listed in Table I. Discontinuing the drug usually leads to rapid improvement of the clinical symptoms, whereas clearing of the serologic abnormalities occurs later. The ANA level typically remains elevated after symptoms have resolved for an average of 4 months.

DIFE is probably mediated by reactive drug metabolites, not the ingested medications, and susceptibility to neutrophil-mediated oxidative transformation is a property of drugs, such as procainamide, hydralazine, quinidine, and et al. Although the pathogenesis of LE induced by fluorouracil agents remains unknown, several hypotheses have been proposed. In the epidermis, basal cells are undergoing active mitosis and are susceptible to damage by fluorouracil agents. The damaged basal cells may be more sensitive to ultraviolet light irradiation, which induces liquefaction changes and patchy lymphocytic infiltration. The nuclear antigens released by damaged basal cells may sensitize the immune system, and induce ANAs.

To the best of our knowledge, this is the first reported case of LE-like skin lesions induced by UFUR in Taiwan. UFUR should be considered as a possible cause of a LE-like skin lesion during UFUR therapy. The drug should
be discontinued immediately at the onset of LE-like skin lesions followed by appropriate investigations including histologic and immunofluorescence examinations, autoantibody screening such as ANAs, anti-Ro, anti-La, antihistone antibodies to establish the diagnosis. In addition, use of short-term, low dose steroids may be indicated for those with manifestations of DILE.

REFERENCE
Familial Atrophia Maculosa Varioliformis Cutis
- Case Report -

Chung-Chu Wang     Pei-Lun Sun     Yu-Hung Wu     Yang-Chih Lin

Atrophia maculosa varioliformis cutis was first described by Heidingsfeld in 1918 as the gradual, spontaneous appearance of painless, shallow, sharply demarcated depressions of various shapes on the face. To the best of our knowledge, only 17 additional cases have been reported since the first description. We describe the first two patients in Taiwan. They are a sister and brother, aged 10 and 8 years, with multiple, spontaneous, randomly scattered, asymptomatic, atrophic lesions on the cheeks and chin. They had no history of varicella or acne. Histopathologic examination of an incisional biopsy specimen showed an unremarkable epidermis. In the upper dermis, there were a few compact collagen bundles and decreased elastic fibers. It is essential to differentiate this entity from scarring, artifact dermatitis, or atrophoderma vermiculata. We have suggested that the family consider dermabrasion for the disorder once the children reach adulthood. (Dermatol Sinica 22: 178-182, 2004)

Key words: Atrophia maculosa varioliformis cutis, Atrophoderma vermiculata

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INTRODUCTION

Atrophia maculosa varioliformis cutis (AMVC) is a rare and distinctive form of idiopathic noninflammatory facial macular atrophy.\(^1\) It is important to distinguish it from scarring, artifact dermatitis, and atrophoderma vermiculata.\(^2\) We report the first two cases in Taiwan and review the literature to date.

CASE REPORTS

Case 1. A 10-year-old girl was brought to our Dermatologic Clinic for evaluation of multiple, randomly scattered, asymptomatic, atrophic lesions on her face. They were mostly on the cheeks, with a few on the chin and had been present for about 5 years. They appeared spontaneously and had increased slowly in number and size. The lesions were oval to round in shape and approximately 1 to 3 mm in diameter (Fig. 1). There was no erythema or other pigmentary change, scale, or herniation. Her parents stated that she had no history of previous inflammatory lesions on her face, scarring after chicken pox, acne, or facial trauma. She was physically and mentally healthy. Histopathologic examination of an incisional biopsy specimen from the right cheek demonstrated a generally normal looking epidermis. There were focal

![Fig. 1](image1)

Case 1: The lesions were oval to round in shape and approximately 1 to 3 mm in diameter.

![Fig. 2](image2)

Histopathologic examination demonstrated a generally normal looking epidermis and compact collagen bundles focally in the upper dermis.

![Fig. 3](image3)

There were decreased numbers of elastic fibers as seen with Verhoeff-van Gieson stain.

![Fig. 4](image4)

Case 2: A few varioliform macular atrophic lesions resembling those observed in his elder sister were present.
areas of compact collagen bundles in the upper dermis (Fig. 2) and decreased numbers of elastic fibers as seen with Verhoeff-van Gieson stain (Fig. 3).

Case 2. The younger brother of patient 1, aged 8 years, had had similar asymptomatic depressions on his cheeks for about 3 years. He had no history of varicella or acne, and the depressions had appeared without any preceding inflammation. On examination, a few vario-

liform macular lesions resembling those observed in his elder sister were present (Fig. 4). He was in good physical and mental health. Although no skin biopsy was performed, the diagnosis of AMVC was made based on the clinical presentation and family history.

DISCUSSION

Table I. Clinical features in reported cases of AMVC

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patient Age (yr)</th>
<th>Patient Sex</th>
<th>Duration (yr)</th>
<th>Family history</th>
<th>Lesion characteristics</th>
<th>Preceding inflammation</th>
<th>Associated findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heidingsfeld</td>
<td>1918</td>
<td>20 M</td>
<td>1.5</td>
<td>-</td>
<td>-</td>
<td>Cheeks</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Senear</td>
<td>1923</td>
<td>18 F</td>
<td>0.5</td>
<td>NA</td>
<td>NA</td>
<td>Cheeks, forehead</td>
<td>-</td>
<td>Mild acne*</td>
</tr>
<tr>
<td>McCorriston and Roys</td>
<td>1951</td>
<td>37 F</td>
<td>1.3</td>
<td>-</td>
<td>+</td>
<td>Cheeks, chin</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Marks and Miller</td>
<td>1986</td>
<td>22 M</td>
<td>1.3</td>
<td>+</td>
<td>+</td>
<td>Radiating from mouth, jawline</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Marks and Miller</td>
<td>1986</td>
<td>18 M</td>
<td>NA</td>
<td>+</td>
<td>+</td>
<td>Cheeks</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Venencie et al.</td>
<td>1989</td>
<td>9 F</td>
<td>1</td>
<td>-</td>
<td>+</td>
<td>Cheeks</td>
<td>-</td>
<td>Biliary atresia</td>
</tr>
<tr>
<td>Kolenik et al.</td>
<td>1994</td>
<td>14 F</td>
<td>1</td>
<td>-</td>
<td>+</td>
<td>Cheeks</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kolenik et al.</td>
<td>1994</td>
<td>14 F</td>
<td>1</td>
<td>-</td>
<td>+</td>
<td>Cheeks</td>
<td>-</td>
<td>Mild acne*</td>
</tr>
<tr>
<td>Nakayama et al.</td>
<td>1994</td>
<td>15 F</td>
<td>A few</td>
<td>-</td>
<td>+</td>
<td>Cheeks</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kolenik et al.</td>
<td>1994</td>
<td>14 F</td>
<td>1</td>
<td>-</td>
<td>+</td>
<td>Cheeks</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nakayama et al.</td>
<td>1994</td>
<td>15 F</td>
<td>A few</td>
<td>-</td>
<td>+</td>
<td>Cheeks</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Callot et al.</td>
<td>1995</td>
<td>22 M</td>
<td>NA</td>
<td>-</td>
<td>+</td>
<td>Cheeks</td>
<td>-</td>
<td>Pachydermodactyly</td>
</tr>
<tr>
<td>Gordon and Doherty</td>
<td>1996</td>
<td>15 F</td>
<td>12</td>
<td>+</td>
<td>+</td>
<td>Under the chin</td>
<td>-</td>
<td>Varicella*</td>
</tr>
<tr>
<td>Gordon and Doherty</td>
<td>1996</td>
<td>13 F</td>
<td>0.5</td>
<td>+</td>
<td>+</td>
<td>Periumbilical to post pinna</td>
<td>-</td>
<td>Molluscum*</td>
</tr>
<tr>
<td>Dall'Oglio et al.</td>
<td>2001</td>
<td>14 M</td>
<td>A few months</td>
<td>+</td>
<td>-</td>
<td>Cheeks, forehead</td>
<td>-</td>
<td>Varicella*</td>
</tr>
<tr>
<td>Dall'Oglio et al.</td>
<td>2001</td>
<td>16 M</td>
<td>2</td>
<td>+</td>
<td>-</td>
<td>Cheeks, forehead</td>
<td>-</td>
<td>Varicella*</td>
</tr>
<tr>
<td>Paradisi</td>
<td>2001</td>
<td>5 M</td>
<td>3</td>
<td>-</td>
<td>+</td>
<td>Cheeks</td>
<td>-</td>
<td>Varicella*</td>
</tr>
<tr>
<td>Kalayciyan</td>
<td>2003</td>
<td>21 F</td>
<td>2</td>
<td>+</td>
<td>+</td>
<td>Cheeks</td>
<td>-</td>
<td>Varicella*</td>
</tr>
<tr>
<td>Kalayciyan</td>
<td>2003</td>
<td>23 M</td>
<td>3</td>
<td>+</td>
<td>+</td>
<td>Cheeks</td>
<td>-</td>
<td>Varicella*</td>
</tr>
<tr>
<td>Current report</td>
<td>2003</td>
<td>10 F</td>
<td>5</td>
<td>+</td>
<td>-</td>
<td>Cheeks, chin, forehead</td>
<td>-</td>
<td>Varicella*</td>
</tr>
<tr>
<td>Current report</td>
<td>2003</td>
<td>8 M</td>
<td>3</td>
<td>+</td>
<td>+</td>
<td>Cheeks, chin</td>
<td>-</td>
<td>Varicella*</td>
</tr>
</tbody>
</table>

Modified from Kolenik et al.7
NA: not available; +: positive; -: negative
* Not present at sites of AMVC
Since Heidingsfeld first described AMVC in 1918, only 18 cases have been reported (Table I). AMVC is characterized by the spontaneous appearance in young individuals of round, oval, linear or rectangular macular atrophy on the cheeks and forehead, without any inflammation. The etiopathogenesis is unknown, although familial occurrence has previously been reported in eight patients to date, suggesting an inherited disorder rather than a response to an environmental insult.1, 3 The familial occurrence in siblings only and its appearance in childhood suggest an autosomal recessive mode of inheritance.1 Cases associated with extrahepatic biliary atresia, pachydermodactyly and keratosis pilaris have been described, but the associations may be coincidental.

The diagnosis of AMVC is largely made clinically in the presence of macular depressions on the face with sharply demarcated edges and the absence of erythema, induration, pigmentedary change, or herniation.8,9 Histopathologic findings are nonspecific, with a relatively normal dermis, compact collagen bundles, slightly decreased elastic fibers, no fibrosis, and few or no inflammatory cells below a shallow depression of the epidermis (Table II).

An ultrastructural study of the skin in one patient showed an abnormal amount of exuberant elastin and the deposition of abundant collagen fibrils of normal size and shape arranged in compact bundles in the dermis, resulting in a relative decrease in the extracellular matrix component.3 The presence of hyperactive fibroblasts seems to suggest active synthetic activity in focal areas of the dermis.3 The obvious epidermal retraction may be due to increased collagen content or, alternatively, a reduction in extracellular matrix proteoglycans and, consequently, decreased dermal hydration.3

Varicella, acne, or trauma can be excluded by the absence of any preceding inflammatory condition plus the finding of dermal fibrosis on
biopsy. The absence of fibrosis is crucial for differentiating AMVC from scarring. This finding in our first patient, plus a normal psychological evaluation, convinced us that she did not have scarring from accidental trauma or abuse. We excluded the diagnosis of atrophoderma vermiculata because of the appearance of the lesions; they were extrafollicular but not in a reticular pattern as seen in atrophoderma vermiculata. Atrophoderma vermiculata is histopathologically distinguished by the presence of dilated hyperkeratotic follicles and by dermal cysts and is considered to belong to the keratosis pilaris group of disorders. We further excluded keratosis pilaris atrophicans because of the absence of erythema and follicular hyperkeratosis.

No specific therapy has been suggested for AMVC. Collagen injections, dermabrasion, or laser resurfacing may theoretically help. Understanding the etiology of AMVC will likely require the finding of more cases.

REFERENCES