course of prednisolone (40, 30, 20 mg/day). When prednisolone was tapered to 15 mg/day, erythematous macules and plaques recurred, initially over the trunk, with a high-grade fever. Despite apparent signs of deterioration of her erythema, oral prednisolone continued to be tapered. As a result, the erythematous macules rapidly increased in number and progressed to involve the entire body. She was eventually referred to us and the diagnosis of TEN was made. She developed numerous targetoid lesions over the entire body with bullous lesions. On admission to our department, her respiratory status remained stable and the pneumonia had cleared radiologically. Ophthalmologic investigation documented a bilateral mild conjunctivitis. Touching her skin lesions caused painful sloughing and bleeding. Although her prednisolone dose was increased to 50 mg/day, the low fever persisted and epidermal detachment of more than 80% of the body surface with widespread macules was noted. On the 8th hospital day, conventional PP was initiated. The fever resolved within 24 h and within 3 days skin lesions had sufficiently improved; the patient received one session of two exchanges over 7 days. On day 16, she made an excellent recovery with almost resolution of the skin lesions (Fig. 4). Although culture and direct molecular detection by polymerase chain reaction were unavailable, results of serological studies of this patient disclosed a significant rise in *M. pneumoniae* PA and CF antibodies and positive immunoglobulin (Ig)M antibody, consistent with an active *Mycoplasma* infection. She remained free of symptoms for 6 months without any treatment.

Case 4

A 48-year old woman with ulcerative colitis presented with 4 days' history of fever and a rash that began on her breast and then spread to the extremities and face. She had been treated with salazosulfapyridine. One day before admission, she experienced high fever, generalized erythematous raised atypical targets and small blisters in the center of these lesions. On physical examination, she had bilateral corneal erosions, eroded lips with overlying hemorrhagic crust and oral ulceration with overlying white exudates. These lesions progressed over 2 days to become a widespread, confluent erythema, with a positive Nikolsky's sign. She was

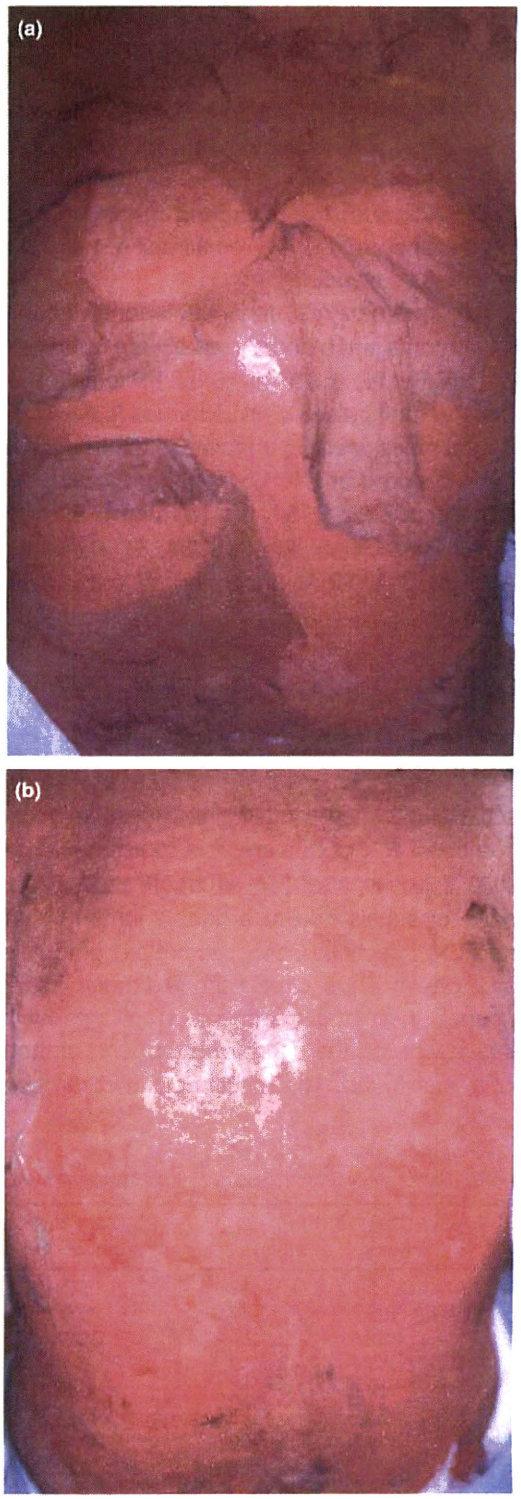

Figure 4. Clinical appearance 2 days before conventional plasmapheresis (PP) (a) and 2 days after conventional PP (b) in case 3.

treated with pulsed corticosteroids. Over the next few days, her condition slightly improved but new erythematous lesions occurred. The patient was again treated with pulsed corticosteroids. The skin lesions improved, showing re-epithelization and never progressed to extensive full thickness skin detachment. Later, the dosage of prednisolone was gradually tapered and the remainder of her hospital course was uneventful.

These four patients underwent serial laboratory measurements and blood samples were obtained just before the first PP and after the last PP (cases 1–3), or before and after pulsed corticosteroids (case 4). Serial blood samples were immediately centrifuged and sera were stored at −80°C. All samples were tested simultaneously for IL-6, -8, -10 and TNF-α levels using cytometric bead arrays (CBA; BD Biosciences, San Diego, CA, USA) according to manufacture's protocol.

CORRELATION BETWEEN DISEASE INTENSITY AND SERUM CYTOKINE LEVELS

Cases 2 and 3 showed a striking clinical response to conventional PP; both were able to return to normal lifestyle 2 weeks after PP, although case 2 had an episode of sepsis due to a double lumen catheter-related line infection. Case 1 improved gradually for up to 2 weeks. Thus, case 1 showed much less striking benefit from the treatment; initial improvement was delayed and the short-lived rebound of the skin lesions was found. The most rapid and remarkable improvement was observed in cases 2 and 3, although they had the most extensive disease. In contrast, cases 1 and 4 treated with DFPP and pulsed corticosteroids, respectively, showed a relatively delayed improvement with occasional formation of new lesions; these lesions had healed completely just 8 weeks after treatment. Oral prednisolone could be tapered more slowly in cases 1 and 4, than that in cases 2 and 3.

During PP treatment, blood counts and coagulant factors were measured. There was no remarkable changes in white blood cell and platelet numbers, coagulation factors and other clinical variables in cases 2 and 3, before and after conventional PP, although the C-reactive protein level after the PP showed a slight reduction. In contrast, a dramatic increase in white blood cell numbers was noted after DFPP in case 1. The fibrinogen levels dropped to 5% of the initial value and it took 3 days to return to normal levels. IgG, A and M levels fell to approximately a fourth of pretreatment concentrations but showed a slower recovery due to their resynthesis (Table 1).

As shown in Figure 5, the serum levels of IL-6, -8 and TNF-α were significantly increased before PP in these patients as compared with those in healthy controls. Conventional PP had a dramatic beneficial effect at reducing these pro-inflammatory cytokine levels in cases 2 and 3, while the unexpected increase in TNF-α and IL-8 levels was observed in case 1 after DFPP. This increase positively correlated with an increase in white blood cell number. In contrast, in case 4 treated with pulsed corticosteroids, a significant decrease in TNF-α levels was noted, but

Table 1. Laboratory findings before and after treatment

	Case 1 (DFPP) before → after		Case 2 (PP) before → after		Case 3 (PP) before → after		Case 4 (mPSL) before → after	
WBC	5.1	16.1	8.2	6.9	12.7	14.9	11.9	11.9
PT	100	17.0	95.0	99.0	94.0	85.0		
APTT	32.5	168.8	33.7	32.6	36.3	38.0		
TP	5.7	3.4	6.4	6.5	5.2	5.3	6.1	6.0
Alb	2.6	2.8	3.0	3.3	2.5	3.2	2.8	2.7
AST	53	15	46	30	9	14	37	24
ALT	111	26	43	37	15	11	50	64
CRP	3.2	0.8	2.5	1.9	1.6	0.5	13.4	3.1
IgG	1480	393	1616	1298	1048	871	1435	1549

WBC, white blood cell; PT, prothrombin time; APTT, activated partial thromboplastin time; TP, total protein; Alb, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; IgG, immunoglobulin G; DFPP, double-filtration plasmapheresis; PP, plasmapheresis; mPSL, methylprednisolone.

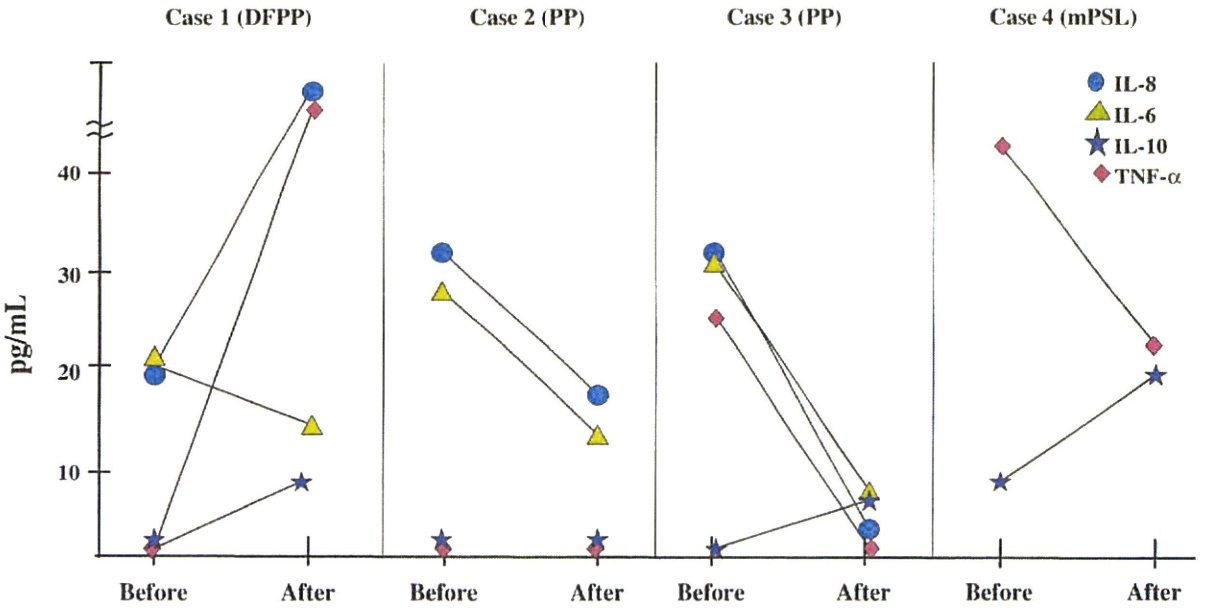

Figure 5. Alteration of serum cytokine levels before and after plasmapheresis (PP) or pulsed corticosteroids. DFPP, double-filtration plasmapheresis; IL, interleukin; TNF, tumor necrosis factor.

its level remained high, as compared with that in healthy controls. Cases 1, 3 and 4 had elevated levels of IL-10 after DFPP, conventional PP and pulsed corticosteroid therapy, respectively. Although there was no statistically significant correlation between IL-10 levels and the extent of clinical improvement, the IL-10 levels tended to increase coincident with clinical resolution.

COMPARISON BETWEEN CONVENTIONAL PP AND DFPP

Although observational studies and case series support the use of either conventional PP or DFPP as the treatment of severe and refractory TEN, no attempts have been made to compare the efficacy of DFPP with that of conventional PP. Based on our results presented here, conventional PP appears to be more efficacious in TEN than DFPP. Treatment with conventional PP is beneficial during the first 2 weeks, but the benefit is likely to be greatest when treatment is given early. Thus, conventional PP can replace DFPP as the preferred treatment for severe TEN. However, concern has also been expressed for many years that FFP used as the replacement solution in conventional PP is a blood product and poses a risk of contamination with infectious organisms despite testing and antiseptic measures to kill or filter them. A catheter-related line infection is a more common complication than is generally realized. However, the risk of a catheter-related line infection in conventional PP is comparable to that in DFPP. Indeed, case 2 developed sepsis despite its remarkable efficacy, after conventional PP. This type of infection was not observed in other cases. The major disadvantage, and the primary reason why DFPP has not been employed in a widespread manner in TEN, are that many pro-inflammatory cytokines responsible for the development of TEN cannot be sufficiently depleted by DFPP because their molecular weights are smaller than the pore size of membrane filters used for DFPP; this is in sharp contrast to pemphigus vulgaris, in which the removal of pemphigus antibodies by DFPP is a reasonable therapeutic approach.[19,20] Therefore, pro-inflammatory cytokines sufficiently removed by DFPP include monocyte colony-stimulating factor (M-CSF) but not IL-1, IL-6 and TNF-α. In support of this possibility, Kodama *et al.*[21] reported that serum levels of IFN-γ, TNF-α, IL-1β, IL-6, and GM-CSF did not decrease after DFPP was started while G-CSF and

M-CSF gradually decreased. Indeed, after the DFPP treatment in case 1, no decrease in any cytokine level was discovered, while slight clinical improvement were found. On the contrary, the highest levels of IL-8 and TNF-α occurred immediately after the DFPP, suggesting the rebound production or release of these cytokines. In view of the fact that either IL-8 or TNF-α can be secreted by neutrophils that accumulate in the circulation after DFPP, the unexpected increase in these cytokine levels might reflect ongoing *in vivo* activation of neutrophils during the process of DFPP. Interestingly, similar, although less remarkable, increase in leukocytes have been reported to occur immediately after blood transfusion but not after plasma infusion.[22]

Because it has been shown that direct contact of blood mononuclear cells with the filter membrane and adherence of platelet to the membrane leads to not only cytokine production but also complement activation,[23] the unexpected increase in white blood cell number after DFPP would result from serum complement activation. Given the ability of neutrophils to respond to these cytokines, the unexpected increase in these cytokine levels after the DFPP appears to result from an *in vivo* positive feedback mediated by the rebound synthesis of these cytokines by activated neutrophils. Alternatively, macrophages would be the major source of these cytokines. However, because these cytokine levels eventually decreased 2 days after the DFPP in patients with bullous pemphigoid (unpubl. data, T. Shiohara, 2010), the rebound of cytokine production would be short-lived. The rebound in cytokine levels after DFPP, but not conventional PP, indicates that the use of FFP during the process of conventional PP would serve to prevent neutrophil or macrophages from secreting more cytokines. Because, in DFPP, original blood cell components initially separated are reconstituted with the processed plasma and replacement solution and returned to the circulation, this process may stimulate neutrophils and macrophages to additionally release these cytokines. Thus, the rebound of cytokine production after DFPP is likely to be the reason why its onset of action is usually delayed after the DFPP and why DFPP is less efficacious in TEN than conventional PP. These results explain why the therapeutic efficacy of DFPP is not high as compared with conventional PP, although theoretically it can selectively reduce toxic substances from the circulation.

EFFECTS OF CONCOMITANT USE OF CORTICOSTEROIDS ON EFFICACY OF PP

Our results indicate that either conventional PP or DFPP modulates the balance between inflammatory and anti-inflammatory cytokines, because the IL-6 levels decreased while the IL-10 level increased after PP except for case 2. Because our patients received 50 mg/day prednisolone during the period of PP (cases 1–3), we cannot exclude the possibility that the combination therapy of PP and prednisolone is key in modulating the cytokine balance in favor of the relative IL-10 dominance. In patients treated with conventional PP, the concomitant use of prednisolone together with FFP may serve to prevent the rebound of cytokine production that occurs normally after DFPP. The additional benefit of conventional PP with the use of FFP as the replacement solution is that there is no significant change in leukocyte populations and coagulation factors while efficiently reducing the levels of inflammatory cytokines.

The rebound of pro-inflammatory cytokine production associated with increased white blood cell counts we observed immediately after DFPP may explain some of the less significant effects of DFPP than those of conventional PP, although DFPP may benefit selected patients with TEN. Because our study indicates that dosage of oral prednisolone was able to rapidly be tapered after conventional PP, we suggest that conventional PP may be an effective adjunct treatment modality in severe and refractory TEN by rapidly reducing inflammatory cytokines without inducing their rebound production. Nevertheless, a mere comparison of treatment efficacy in this study is problematic and might be misleading because only a small number of patients were treated and there were differences in the age of the patients and in the severity of the reactions when the treatment started. According to our data, decreases in pro-inflammatory cytokine levels and increases in IL-10 levels would be a promising marker to identify individuals responding to PP, although this finding will have to be confirmed in larger cohorts. To predict the therapeutic improvement, monitoring of serum cytokine levels may be useful and allow case-by-case therapeutic

management. Because extreme caution on procedural complication such as line infection is needed, this method should only be used as a last resort in patients with TEN refractory to conventional treatments.

OTHER COMBINATION THERAPY WITH PP

Plasmapheresis is usually used for TEN patients refractory to high doses of corticosteroids. Several immunosuppressive agents are also used to treat these TEN patients; they include cyclosporine, tacrolimus, and anti-TNF-α antibodies or soluble TNF receptors to neutralize TNF-α. These agents have been shown to be effective in the treatment of TEN patients.[6,24] Although adding PP to these drugs would also decrease disease severity, there is little available information on this combination therapy.

A tyrosine kinase inhibitor, such as imatinib (Gleevec; Novartis Pharmaceuticals, Basel, Swiss), which is used clinically for patients with chronic myeloid leukemia, would also be effective in reducing inflammation of TEN by reducing TNF-α production.[25] Because this kinase inhibitor has been shown to reduce TNF-α production by human monocytes in response to lipopolysaccharide but not suppress production of an anti-inflammatory cytokine IL-10, it is likely that TEN patients may benefit from this tyrosine kinase inhibitor. Statins can be also used to reduce inflammation in patients with TEN as an adjunct treatment added to PP, because of their widespread use and long-term safety record.

CONCLUSIONS

In Japan, PP is now only used as a last resort in TEN patients who are not responding to the standard therapy, high doses of corticosteroids. It remains unknown, therefore, whether PP alone could prevent severe inflammation in TEN. Although the risk of transmission of endogenous unknown viruses to the patients through FFP have not been totally eliminated, it appears that PP has found a place in the treatment of TEN. Another drawback of PP is a catheter-related line infection that could be treated with antibiotics. Nevertheless, the benefits of PP outweigh these risks: PP appears be a much more effective option for treatment of severe and/or recalcitrant TEN than any other treatments, such as pulsed corticosteroids and IVIG, although the exact mode of action remains unknown. Our data raise the possibility that serum cytokine levels, such as TNF-a, IL-6 and IL-10, before and after PP can serve as predicting markers for its therapeutic efficacy, a hypothesis that requires further testing.

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Cutaneous Granulomatous Reaction After Herpes Zoster in Drug-Induced Hypersensitivity Syndrome

To the Editor:

In the August 2009 issue of this journal, Dr Fernando et al. published a case in the section of Extraordinary Case Report titled "Drug-induced hypersensitivity syndrome (DIHS) with superficial granulomatous dermatitis–a novel finding."[1] We read this article with great interest. In this article, the authors described an impressive case with carbamazepine-induced hypersensitivity syndrome showing unique histopathological findings. The authors speculated that the superficial granulomatous dermatitis observed in the specimen obtained from the rash may have been caused by the persistence of antigenic stimulation from the continued ingestion of carbamazepine in this patient.

Recently, we also observed similar histopathological findings in a patient with carbamazepine-induced hypersensitivity syndrome after a herpes zoster infection. A 69-year-old woman had been treated with carbamazepine 400 mg daily for postherpetic neuralgia. After 10 weeks, a maculopapular rash developed on her left arm. The eruption progressed to diffuse erythema over the trunk and was associated with a high-grade fever. The eruption on her left arm where the herpes zoster lesions had previously developed was remarkably more accentuated than the right arm. Carbamazepine was discontinued, and she was admitted to the hospital with suspected DIHS. Physical examination revealed facial edema and lymphadenopathy. Mucosal involvement was not observed. Laboratory studies revealed leukocytosis with eosinophilia and slight liver dysfunction. Anti-varicella zoster virus (VZV) IgG titer was 121 as determined by an enzyme immunoassay. Anti-human herpesvirus 6 IgG increased from a titer of 40 on admission to a titer of 1280 11 days after admission. A skin biopsy of an erythematous lesion taken from the abdomen showed an accumulation of histiocytic and lymphocytic cells in the upper dermis accompanied by a few eosinophils (Fig. 1A). Granulomatous reactions were observed around the hair follicles and vessels. Positive immunohistochemistry for CD68 confirmed the predominance of histiocytes in the infiltrate (Fig. 1B). Immunohistochemical staining using a monoclonal antibody against glycoprotein 1(gp1) of VZV (Millipore, Temecula, CA.) was carried out because an association between VZV antigens and granuloma formation in hematological disorders has been previously reported.[2] Strong positive staining was detected in the eccrine sweat glands of the specimen (Fig. 1C). Positive lymphocyte transformation test for carbamazepine was obtained at the resolution stage of the disease. Based on these results, the patient was diagnosed as carbamazepine-induced hypersensitivity syndrome. She steadily improved with IV fluid resuscitation for dehydration. A brief description of the clinical course of this patient has been previously published.[3]

The histopathological findings in drug eruptions such as Stevens-Johnson syndrome and toxic epidermal necrolysis are characterized by the specific histological patterns. On the other hand, there are no characteristic features in DIHS. Common histopathological findings taken from an erythematous lesion in patients with DIHS include superficial perivascular lymphocytic infiltrates accompanied by few eosinophils. In some patients, there is liquefaction degeneration of the basal cell layer with a lichenoid infiltrate. Immunohistochemical staining demonstrates a predominance of T cells.[4] Granulomatous reactions in DIHS have rarely been detected.

The causative drugs of DIHS include aromatic anticonvulsants such as carbamazepine, phenytoin, and phenobarbital. Interestingly, Magro et al[5] reported that such anticonvulsants could induce interstitial granulomatous drug reaction characterized by histiocytic infiltration in the connective tissue. Fernando et al[1] speculated that granulomatous inflammation may have resulted from sustained exposure to carbamazepine, which is a known causative drug of interstitial granulomatous drug reaction.[5] Considering that carbamazepine is the most commonly implicated drug for DIHS,[6] and that granulomatous reactions have rarely been observed in patients with DIHS, it is likely that factors other than the protracted administration of carbamazepine contributed to the development of granulomas in DIHS. F1

Interestingly, in the present patient, VZV reactivation preceded the development of DIHS. With respect to the association between VZV and granuloma formation, the previous documents have demonstrated that granulomatous reactions are frequently observed in patients with hematological disorders as the postherpetic granuloma.[2,7] In this setting, the average interval between the herpes zoster infection and the appearance of granulomas is 6 months; the altered immune reactions have been suggested to be responsible for the development of granuloma. In the present patient, the granulomas appeared 3 months after the onset of herpes zoster, a time frame that is similar to the postherpetic granuloma. In addition, the immunological alterations such as decrease in peripheral B-cell counts and reduction in serum immunoglobulin levels are detected at the onset of DIHS.[8] It is, therefore, likely that they have some similar underlying pathomechanisms in common. Thus, the preceding herpes zoster infection that might have disseminated zoster lesions could have played an important role for the development of granulomatous reactions in our patient.

In summary, our case raises the possibility that VZV reactivation might

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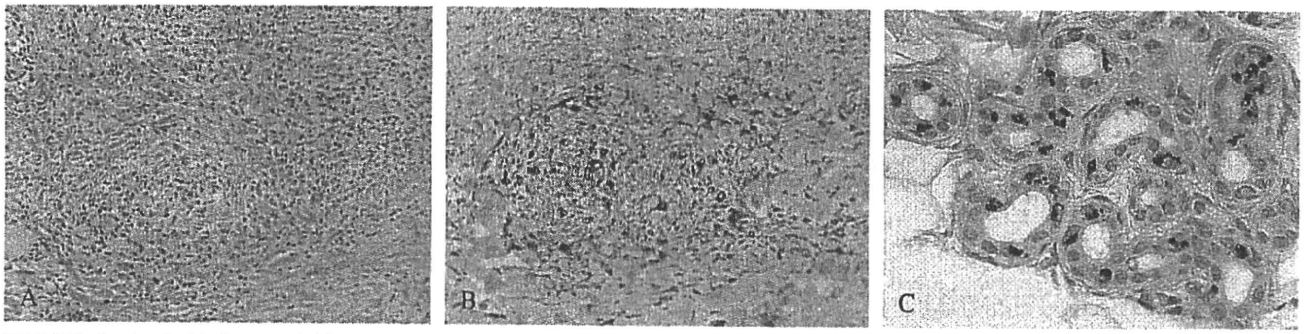

FIGURE 1. A, A histiocyte infiltrate accompanied by lymphocytes in the upper dermis (hematoxylin–eosin stain, original magnification ×200). B, The infiltrate was mainly composed of CD68-positive cells (original magnification, ×200). C, Immunohistochemical detection of glycoprotein 1 of VZV in eccrine sweat glands (original magnification, ×400).

contribute to the subsequent development of granuloma in patients with DIHS.

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EL28—2　軟膏療法の新しい視点

外用療法をもう一度皮膚科医の手に

～経験から科学へ

塩原　哲夫

はじめに

昔，皮膚科の治療と言えば外用療法が主体であった．外用薬を工夫することによって，難治な皮膚疾患を治すことこそ皮膚科の醍醐味であった．しかし，ステロイド外用薬（ス剤）の登場以降，その効果の強さ故，他の外用薬は殆ど使われなくなり，いつの間にか外用療法の工夫と言えば，どんなス剤を使うか，どうやって他剤と混合するか否かと言ったレベルの話になってしまった．ス剤を使うだけなら，他科の医師が処方しても十分効果があるわけで，皮膚科医の優位性を保つのは難しくなるのは当然である．皮膚科医自身が外用療法の重要性に目覚め，もう一度外用療法に独自の工夫を加えていかねば，皮膚科医は生き残っていけないであろう．しかし，それは過去の外用療法に戻れ，といった後ろ向きの話であってはならない．今こそ，従来の経験に基づいた外用療法を脱し，科学的なエビデンスに基づいた新しい外用療法を皮膚科医自身が打ち立てねばならない．

1．外用療法の基本

外用療法の基本は“湿潤していれば乾かせ”，“乾いていれば湿らせる”ことに尽きる．しかし今，皮膚科医の多くはこの簡単な原則を忘れている．この症例1（図1）は半年以上多くの皮膚科専門医にかかりながら，ステロイド，プロトピック®，亜鉛華軟膏を処方され続けていた．診断は酒皶様皮膚炎であるが，どこでもローション基剤の処方はなされていなかった．この症例は確かに顔には脂漏が目立ったが，逆に体は極めて乾燥しており，このバランスの悪さこそ是正しなければならないと考えた．そこで，顔面にイオウカンフルローションを処方する一方で，体に保湿剤を多量に外用してもらうことにした．その結果，顔と体の角層の水分量のバランス（発汗のバランス）が改善され，顔面の皮疹は著明に改善したのである．

一方，症例2（図2）は左側のみに乾燥性湿疹を有する患者である．この症例では左側のみ発汗低下があるため乾燥性湿疹を生じていたのである．しかるに，近医よりス剤のみが処方されていたため，ますます角層水分量が低下し増悪していた．そこでス剤を中止し保湿剤だけを多量に外用させたところ，それだけで軽快したのである．

類乾癬と言えば治療としてス剤の外用の他に紫外線療法など免疫抑制療法が考慮されるであろう．しかし，症例3（図3）はそれらの治療に全く反応しなかった．こういった症例では病変部の発汗が著明に低下しており，非病変部ではその代償として著明に発汗が亢進していた．このような発汗のアンバランスこそ，皮疹が軽快しない理由なのだという視点を忘れてはならない．この症例に対しても保湿剤を多量に外用させたところ，4カ月で発汗のアンバランスが是正され皮疹は著明に軽快した．

2．角層水分量が接触過敏反応の程度を決める

保湿剤がス剤より炎症性皮膚疾患に効くというのは，俄に信じがたいことかもしれない．それは皮膚の炎症を抑えるのに，角層の水分量だけ増やしても関係ないはずだという思い込みから来ている．そこで，保湿剤がこれだけ多くの炎症性皮膚疾患に奏効するのなら，角層水分量を増やすだけで皮膚の炎症が低下するかもしれないと予想し，動物実験で確認してみようと考えた．

BALB/cマウスはハプテン塗布による接触過敏反応（CHS）を強く生じ，Th2反応も起こしやすいマウスであるのに対し，C57BL/6（B6）はCHSの程度が弱くTh2反応も起こしにくい系統である．しかし面白いことに，この両者のマウスの皮膚の角層水分量にはかなりの差が見られる．BALB/cは水分量が極めて低いのに対し，B6では高値となる．これはまさにCHSの強さが，角層水分量に反比例する可能性を示している．そこで，水分量の低いBALB/cマウスを高湿度環境

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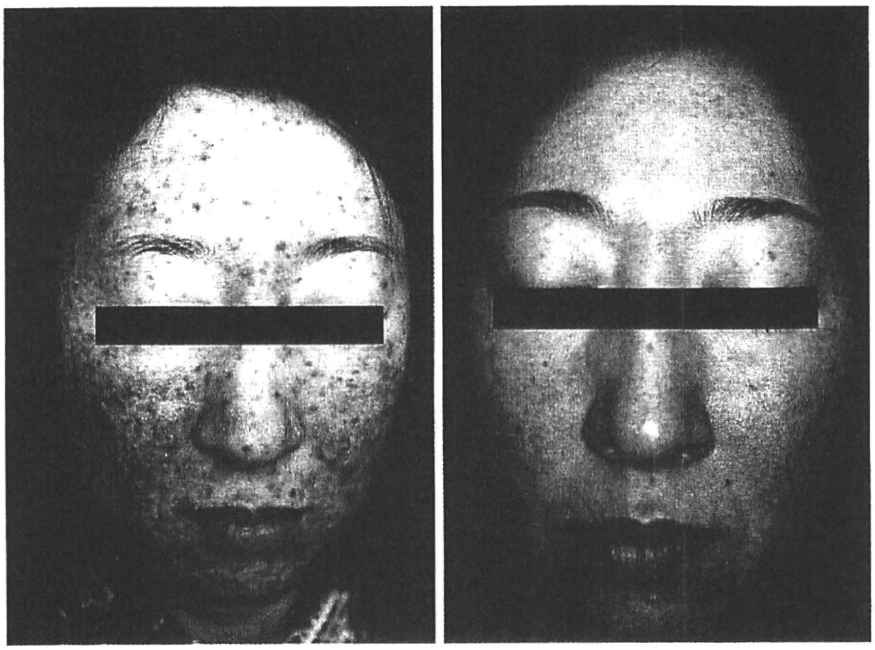

図１ 症例１に対してイオウカンフルローション使用前（左）と使用後（右）

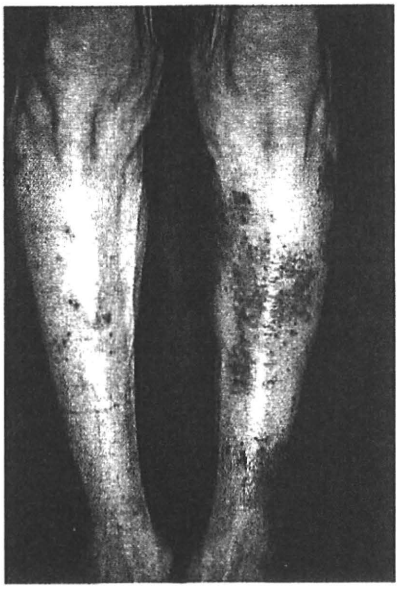

図２ 症例２では左側のみに乾燥性湿疹を認める

（>80% 相対湿度）において誘発すると，CHS が有意に低下し，通常湿度（40～60%RH）環境下での B6 マウスの CHS と差がなくなってしまうのである．この結果は，角層水分量を増やすだけで，湿疹を起こしやすい人でも起こしにくくなることを示している．

3. 新しい薬剤の使い方

イミキモドは Toll-like receptor 7 を刺激することにより皮膚に炎症反応を起こし，ウイルス性疾患や皮膚癌を退縮させる全く新しいタイプの外用薬である．ボーエン病に使用すると著明な苔癬型組織反応（LTR）を生じ，腫瘍細胞が消失（図 4）する．図 4 右のみの組織をみると，典型的な LTR を呈していることが分かる．つまり，我々がしばしば経験する LTR の多くは，このようにしてウイルスや腫瘍に対して生体が起こした自然免疫反応に他ならないといえよう．もしそうなら，LTR の治療としてステロイドやタクロリムスなどの免疫抑制薬を使うということは，自然に起こっている抗ウイルス，抗腫瘍反応を抑制していることになるのかもしれない．実際に，扁平苔癬から癌が発生したとの報告もある．もしそうなら，難治性の扁平苔癬の治療としてイミキモドを使用するという選択もありうることになる．

4. これからの皮膚科医が目指す外用療法

最近の皮膚科医は，患者の皮膚に触れることが極端に少なくなった．触ってみるだけで，皮膚の水分量だけでなく皮膚温，表面の荒れを手で感ずることが出来るのに，である．症例 1, 2 のように部位により水分量の差が著明にある場合には，何も角層水分量を測定しなくても手で触れるだけで分かる．皮膚科医は積極的に患者の皮膚に触れて，自らの五感を高め，皮膚科の職人力を高めるべきである．

その一方で，皮膚科医には病変部で何が起こってい

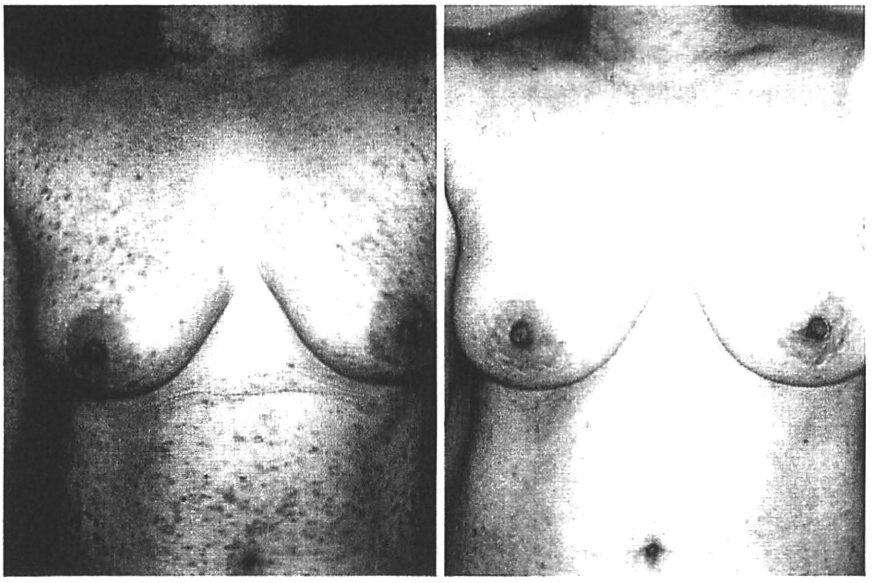

図３　症例３（類乾癬）の保湿剤外用前（左）と外用後（右）

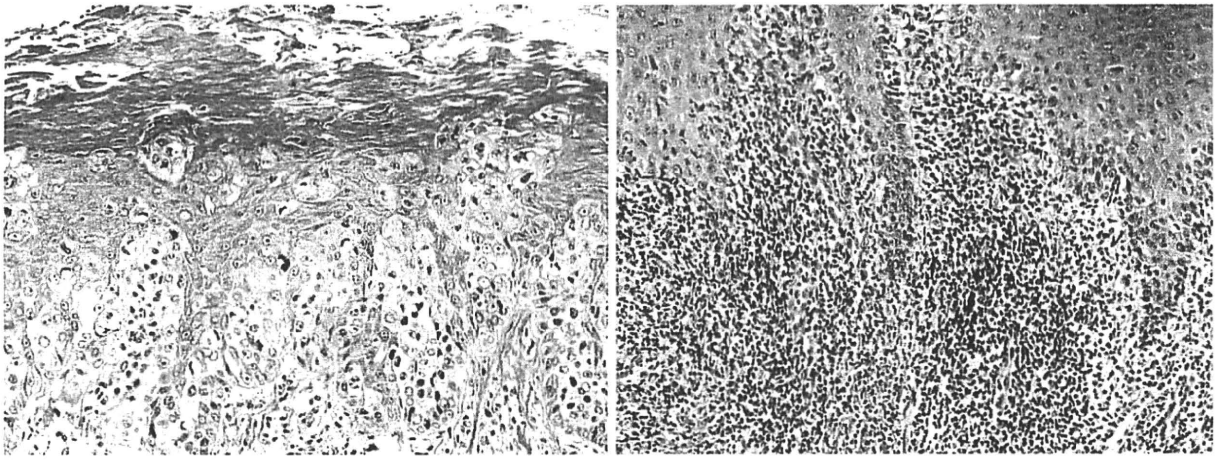

図４　ボーエン病に対するイミキモド外用前（左）と外用後（右）

るかを推測する科学力も必要になる．何もサイトカインをいちいち測定しなくても，病理組織標本を見るだけで，どのようなサイトカインが出ているかを推測出来るだけの科学力をつけねばならない．一方で，その推測が正しかったかどうかを検証することも必要である．非侵襲的な方法で皮膚の水分量だけでなく，硬さ，弾力，色調などを測定し，そのデータを元に，皮膚の内部で起こっていることが推測出来れば理想的である．

以上のことが出来て初めて，最も適した外用薬を選択することが可能になるはずである．その場合，保険適応となっている外用薬を機械的に選択するのではなく，保険適応からすると一見矛盾したような外用薬(先程述べた炎症性疾患に対するイミキモドのような)も，症例を選べば有効である可能性も出てくる．そのようにして，治療薬を選択していく場合には，保険適応となっている外用薬を選択するのと違って，ある程度の決断力も必要となる．このような増悪させてしまうリスクのある保険外使用は余程確信がなければ行うべきではない事はもちろんである．

最終的には，治療効果から自らの推測の正しさ（誤り）を検証するという謙虚な姿勢も必要となる．

おわりに

外用薬を上手に使うことで，いくら強力なス剤を使用しても治らなかった症例が治った時ほど，皮膚科医としての喜びを感じることはない．これらの若い皮膚科医には，従来の外用療法を踏襲するのでなく，科学的エビデンスに基づいた新しい外用療法を開発していく責任がある．さもなければ，皮膚科医に明るい未来はない．

Case and Review

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Lichen Planus Occurring after Influenza Vaccination: Report of Three Cases and Review of the Literature

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Key Words
Linear lichen planus · Influenza vaccination · Hepatitis C

Abstract
Although influenza vaccine is thought to be effective and safe, it occasionally causes systemic reactions such as toxic epidermal necrolysis, bullous pemphigoid, lichen planus (LP), etc. The period of increased risk of developing these events was different depending on the immune responses induced by the vaccination. We report 3 cases of LP which appeared after an influenza vaccination. Our cases indicate that the period of increased risk of developing vaccine-related LP was concentrated within 2 weeks after vaccination, and that the vaccine alone represents a triggering factor necessary for immune alteration sufficient for the development of LP. Because these adverse events tend to develop over a predictable time course, the time of onset may give an important clue to the diagnosis of vaccine-related diseases. We suggest that a history of recent vaccination should be sought in all patients presenting with linear LP.

Introduction

The small risk associated with vaccination is more important among otherwise healthy adults, in whom the magnitude of benefit from vaccination is relatively lower than in those at increased risk for severe influenza and its complications as a result of age or underlying medical conditions. An influenza vaccine often causes local reactions, such as induration and erythema at the injection site, and occasionally systemic reactions; the latter reactions include toxic epidermal necrolysis (TEN), bullous pemphigoid, lichen planus (LP) and so on [1–10]. The association between these reactions and the influenza vaccine, however, has not been widely recognized. We report 3 cases in whom LP appeared within 2 weeks after influenza vaccination.

Case Reports

Case 1

A previously healthy 71-year-old woman received an inactivated influenza vaccine (Kaketsuken Astelas) in the left arm. Seven days after the injection, erythematous-to-purple, slightly raised papules developed on her left buttock. The eruption gradually spread downwards to part of her thigh (fig. 1a), forming a linear distribution. The linear skin lesions appeared to follow the lines of Blaschko or a dermatomal distribution. There was no oral involvement or rashes at the injection site. Hepatitis serology workup revealed negative hepatitis B surface antigen, and positive hepatitis C virus (HCV) antibodies. HCV RNA viral load counted 3,100 kIU/ml. She had had 3-yearly influenza vaccinations; in the 3 years, 1 week after the vaccination, she had always developed herpes zoster at different sites, clearly crossing dermatomal distributions. We therefore measured varicella zoster virus IgG titers on 2 occasions, at the initial presentation and more than 3 weeks after the initial presentation; however, no significant increases were detected. On clinical examination, the lesions were mainly located on the left leg in a striking linear pattern extending from the left buttock down the posterior aspect of the thigh and the leg. A skin biopsy specimen obtained from the lesion showed hyperkeratosis, apoptotic cells, exocytosis in the epidermis, liquefaction at the dermoepidermal junction and band-like mononuclear cell infiltration in the upper dermis (fig. 1b).

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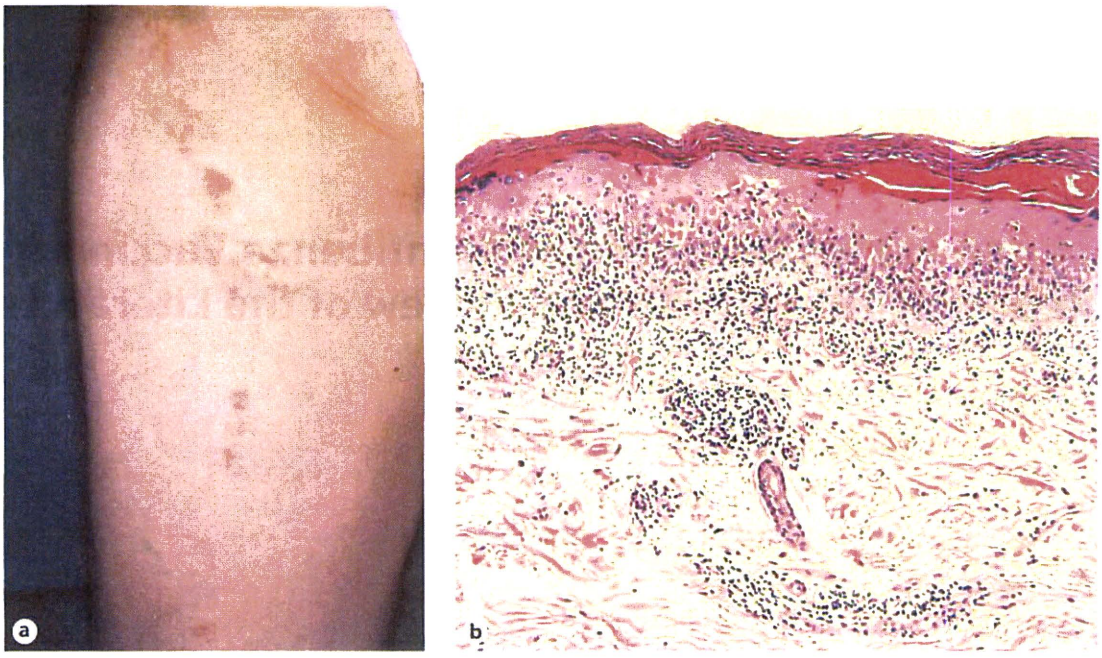

Fig. 1. a Erythematous, slightly raised papules from the left side of the hip to the lower part of the thigh in case 1. **b** Histological findings of the raised papule in the lower part of the thigh. Slightly hyperkeratotic epidermis with a lichenoid inflammation in case1. HE. Original magnification: ×100.

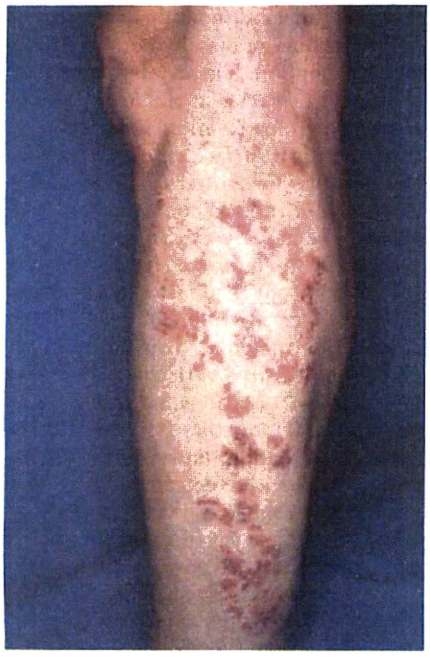

Fig. 2. Itchy, erythematous papules on the left leg in case 2.

Routine laboratory tests were within normal ranges. On the basis of the clinical and histological findings, we diagnosed this case as linear LP. After a month of treatment with topical corticosteroid (diflucortolone valerate), the eruption gradually resolved and finally disappeared, leaving slight pigmentation. The patient had had a recurrence in the same area 1 week after the influenza vaccination in the next year.

Case 2

A 70-year-old woman received the inactivated influenza vaccine. Two weeks after the injection, itchy, erythematous papules developed on the left leg (fig. 2). The lesions gradually increased in number and size, following the lines of Blaschko or a dermatomal distribution. No oral lesions were observed. Neither hepatitis B virus (HBV) nor HCV infection was detected. A skin biopsy showed a lichenoid tissue reaction consistent with LP. According to the histological and clinical findings, we diagnosed this case as linear LP. The patient was treated with topical corticosteroid (clobetasol propionate). After 6 months, the eruption was completely suppressed.

Case 3

A 46-year-old woman received the inactivated influenza vaccination. Two weeks after the injection, lacy white plaques and erosions on both buccal mucosae appeared and spread. She had neither dental alloys nor dental fillings. She had not received any medical treatment for any diseases before the injection. A test for oral fungal infection was negative. HBV or HCV infection testing was negative. A biopsy specimen obtained from the buccal mucosa showed basal cell liquefaction with band-like lymphocytic cell infiltration, consistent with oral LP. During the follow-up period of 1 year, the eruption had gradually disappeared with topical corticosteroid (dexamethasone).

Discussion

Because there are no general criteria for attributing adverse events to a vaccine, these events should be assessed on a case-

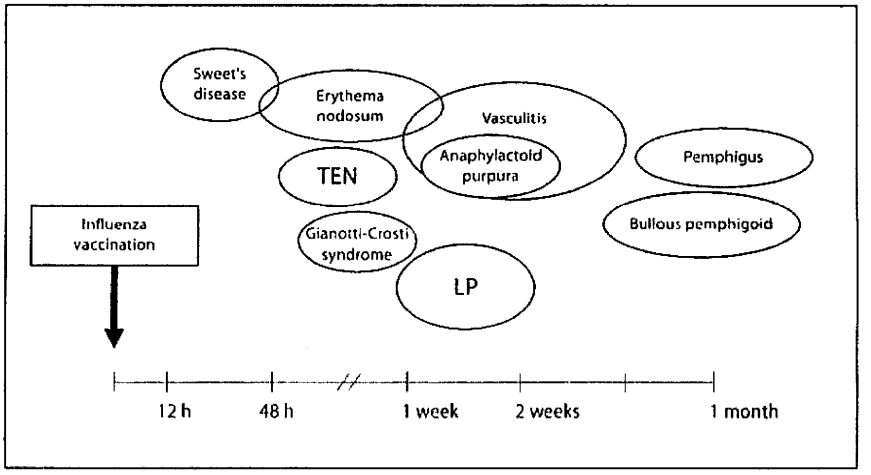

Fig. 3. Various skin diseases develop over a predictable time course after influenza vaccination.

by-case basis. An adverse event can generally be said to be caused by a vaccine if there is a clear temporal relation between vaccination and the adverse event, or if it is associated with a special clinical syndrome such as Guillain-Barré syndrome and influenza vaccine [11]. Many reports have documented the occurrence of LP after administration of different types of HBV vaccines [12–14]; the time interval between the injection and the development of LP lesions ranges from a few days to 3 months. The form observed in HBV-induced LP is usually eruptive. Mucous membranes may or may not be involved; no alterations to the nails have been reported. As far as we know, 27 cases of LP developing after vaccination have been documented in the English literature. Among them, all cases but 1 were LP following HBV vaccination. One potential mechanism is molecular mimicry. According to this theory, HBV vaccines possess antigenic determinants that can also be recognized by the host immune system. Evidence in support of such cross-reactive immune responses between shared antigenic vaccine epitopes and keratinocytes has previously been provided [12–14]. In contrast, LP occurring after influenza vaccination has only been reported in 1 case [10]. Given the frequency of individuals having been vaccinated against influenza in many parts of the world, the risk of the development of LP as a result of vaccination with current inactivated influenza vaccines would be extremely low.

On the other hand, there are numerous reports of various skin diseases that developed after influenza vaccine injection [1–10]; they include TEN, Sweet's disease, erythema nodosum, Gianotti-Crosti syndrome, vasculitis, bullous pemphigoid, pemphigus and LP (fig. 3): the period of increased risk of developing these adverse events was different depending on the immune responses induced by influenza vaccination. Vaccine-associated diseases previously reported can be divided into 3 groups: very early (approx. 48 h), early (approx. 2 weeks) and late (>2 weeks), depending on the time interval between vaccination and the development of the diseases. For example, the onset of Sweet's syndrome is concentrated primarily 12–48 h after the vaccination [1–3]. Erythema nodosum and TEN tend to appear within 1 week after the vaccine [8, 9]. In contrast, the onset of bullous pemphigoid and pemphigus is mainly observed 1–3 months after vaccination [4–6]. This delay would represent the latent period that is needed to synthesize autoantibodies, although this association has not been supported by a recent study [15]. Interestingly, our 3 patients developed LP within 2 weeks after the influenza vaccine, indicating that the period of increased risk of developing vaccine-related LP is concentrated primarily within the 2 weeks after vaccination, which is consistent with the result of the previous report [10]. Thus, it seems unlikely that the appearance of LP in our cases is coincidental. The time of onset of these adverse events may give an important clue about the diagnosis of vaccine-related diseases. Our findings can also be interpreted to indicate that the vaccine-related risk of developing LP may be much lower than the risk after the corresponding natural infection. If so, careful attention should be paid to the possibility that predisposed individuals may develop LP within 1–2 weeks after natural infection with influenza.

Although specific vaccine components that have been implicated in the adverse events include the vaccine itself, residual egg proteins and other additions, specific testing of these vaccine components was unavailable for these patients. Therefore, the possibility remains to be excluded that allergic reactions to either of these components could in part have contributed to the development of LP in predisposed individuals.

There is a continuing controversy as to whether LP is associated with HCV infection [16]. Indeed, case 1 was positive for HCV infection, although the other 2 were negative. These findings suggest that vaccination or HCV alone is not sufficient for the development of LP, but only represents a triggering factor necessary for immune system alteration. It is therefore possible that influenza vaccines acting synergistically with anti-HCV immune responses may have contributed to the development of LP in case 1. An alternative explanation, which we favor, is that LP may have occurred at the site of a previous asymptomatic zoster eruption despite a lack of history of herpes zoster at the site, in view of our findings in cases 1 and 2 that the lesions exhibited a striking linear pattern

suggestive of a dermatomal distribution. In support of this possibility, case 1 had 3 episodes of herpes zoster at different sites 1 week after the vaccination, although this patient did not have serological evidence of previous herpes zoster. Nevertheless, because the absence of serological evidence does not necessarily exclude the possibility of previous herpes zoster, we still infer that subclinical reactivations of varicella zoster virus subsequent to influenza vaccination may be involved in the occurrence of LP in a striking linear pattern. In fact, there have been a few reports on LP occurring at sites of healed herpes zoster [17]. Thus, such adverse events could be caused when associated with other external stimuli or conditions.

We suggest that patients with HCV infection should be carefully observed to detect potentially delayed reactions to the vaccine during a period of 2 weeks. In other words, a history of recent vaccination, particularly a critical 2-week period after vaccination, should be sought for all patients presenting with LP, particularly linear LP.

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Clinical dermatology • **Original article**

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Differences in immunological alterations and underlying viral infections in two well-defined severe drug eruptions

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Summary

Background. Similar drugs (e.g. anticonvulsants) have been implicated in the development of two distinct forms of severe cutaneous drug reactions, Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and drug-induced hypersensitivity syndrome (DIHS)/drug rash with eosinophilia and systemic symptoms (DRESS).

Aim. To investigate immunological alterations and underlying viral infections that could contribute to the variability in the clinical presentations of these diseases.

Methods. We retrospectively analysed clinical variables, serum immunoglobulin levels, numbers of circulating white blood cells, lymphocytes and their subsets, serum levels of several cytokines, and underlying viral infections in both drug reactions, using samples obtained at onset from 9 patients with SJS/TEN and 19 patients with DIHS/DRESS.

Results. There were significant differences between the two drug eruptions in the duration of drug intake before onset, the levels of IgG, IgA and IgM, the numbers of circulating white blood cell, lymphocyte, CD3+ T cell and CD8+ T cells, the serum levels of interferon-γ, and the titres of anti-herpes simplex virus IgG at onset.

Conclusions. The difference in the pattern of immune responses shaped in part by previous and underlying viral infections at the time of drug exposure could cause a marked deviation in the pathological phenotype of severe drug eruptions. Elucidating these host factors may provide a basis for therapeutic approaches in patients with severe drug reactions.

Introduction

Certain drugs, such as anticonvulsants, cause both drug-induced hypersensitivity syndrome (DIHS)/drug rash with eosinophilia and systemic symptoms (DRESS)[1–4] and Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) in different individuals.[5] Many factors can contribute to this variation in drug response, including the dose and duration of drug intake, and the physiological state and genetic background of the patient.[6–8] However, the effect of a history of previous and/or persistent viral infections on subsequent development of drug reactions has received little attention. We recently found that reactivation of human herpesvirus (HHV)-6 contributes to the development of DIHS/DRESS.[4,9,10] Regarding the pathogenetic basis for HHV-6 reactivation, we have also provided evidence that DIHS/DRESS can result when long-term use of drugs such as anticonvulsants, allopurinol and salazosulfapyridine causes a decrease in serum immunoglobulin levels in susceptible patients, thereby facilitating virus reactivation.[4,9,10] To assess whether the host's immune response at the time of onset and any

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underlying viral infections are linked to the variability in the disease course and outcome, we examined clinical and laboratory data of patients with SJS/TEN and DIHS/DRESS.

Methods

The study was approved by the institutional review board at Kyorin University School of Medicine, and informed consent was obtained from all subjects.

Subjects

Data on all patients with a diagnosis of SJS/TEN or DIHS/DRESS who were treated in our hospital between 1998 and 2006 were retrospectively reviewed. Criteria for diagnosis of SJS/TEN were widespread erythematous macules or purpuric macules with irregular shape and size, detachment of skin from > 10% of the body surface area,[11] and involvement of at least one mucous membrane. Criteria for diagnosis of DIHS/DRESS were high fever, a widespread maculopapular and/or diffuse erythematous eruption, lymphadenopathy, leucocytosis with atypical lymphocytosis and/or eosinophilia, and liver dysfunction.[12] There were 9 and 19 patients who satisfied the full criteria for SJS/TEN and for DIHS/DRESS, respectively, and for whom there were sufficient laboratory data, and these were selected for the study.

To identify the causative drug, lymphocyte transformation tests (LTT) were performed using several suspect drugs selected from the multiple drugs taken, based on the temporal relationship between the history of drug intake and the clinical course. However, the timing of testing has been shown to be a crucial factor in the value of LTT, with testing required within 1 week after onset in SJS/TEN and 5–8 weeks after onset in DIHS/DRESS.[13] Patients with DIHS/DRESS underwent testing for serum anti-HHV-6 IgG antibody titres and PCR assays for HHV-6 DNA levels in leucocytes; testing was carried out on sequential blood samples obtained at 2-weekly intervals after onset. HHV-6 reactivation was defined by a > 4-fold increase in anti-HHV-6 IgG antibody titres or detection of HHV-6 DNA in leucocytes.

Almost all blood samples taken for flow cytometry and analyses of serum immunoglobulins, cytokine levels and viral antibodies were usually obtained within 1 week after disease onset, before treatment with systemic corticosteroids was started, but one blood sample in each group was obtained after treatment with systemic corticosteroids had begun.

Serum IgG, IgA and IgM levels in the first samples taken from 9 patients with SJS/TEN and 11 patients with DIHS/DRESS at disease onset were determined by turbidimetric immunoassay. Expression of surface markers, such as CD3, CD4, CD8, CD19 and CD56 on peripheral blood mononuclear cells (PBMC) obtained from nine patients in each group was assessed by flow cytometry (FACS Calibur; Becton Dickinson, San Jose, CA, USA) with Paint-a-Gate software (Becton Dickinson), as described previously.[14,15]

Serum interferon (IFN)-γ, tumour necrosis factor (TNF)-α, interleukin (IL)-2, IL-4 IL-5 and IL-10 were retrospectively measured in the first samples taken from 6 patients with SJS/TEN and 10 patients with DIHS/DRESS at disease onset and stored at −80 °C until tested. The serum levels were measured using a cytometric bead array kit (Becton Dickinson) according to the manufacturer's instructions; simultaneous quantification of these cytokines was made possible using this multiplexed flow cytometric assay.[16,17]

Antibodies to hepatitis B (HBV) and C (HCV) viruses and to human immunodeficiency virus (HIV) were examined for all patients in both groups at first sampling. Anti-HBVe (precore protein) and anti-HBVs (surface antigen) antibodies were further examined in patients with severe liver dysfunction. Antibody titres for human T-cell leukaemia virus (HTLV)-1 and herpes simplex virus (HSV) were also examined by the enzyme immunoassay in 3 and 9 patients with SJS/TEN and in 7 and 10 patients with DIHS/DRESS, respectively.

Statistical analysis

Results are expressed as the mean ± SEM of measurements obtained from 6 to 11 samples that were available for each examination. Statistical comparison between the two groups was performed using the Student *t*-test, with $P < 0.05$ considered significant.

Results

The main clinical data including the underlying illness, causative drugs and the duration of drug intake before the onset of symptoms are summarized in Table 1. An association with anticonvulsants was more common in patients with DIHS/DRESS (15/19 patients; 78.9%) than in patients with SJS/TEN (4/9; 44.4%) although this was not significant (Table 1). No significant difference between the two groups was found for age, gender or associated medical illness. Duration of drug intake before the onset was much shorter in patients with SJS/TEN than in those with DIHS/DRESS (13.8 ± 8.7 days vs. 34.9 ± 8.3 days, $P < 0.05$) (Table 1). Resolution of the eruption occurred in all patients with

Table 1 Characteristics of patients.

Type of drug eruption	SJS/TEN	DIHS
Patients, *n*	9	19
Gender, M/F	4/5	13/6
Age, years; mean ± SD (range)	64.0 ± 6.4† (54–87)	51.8 ± 16.3† (26–73)
Underlying illness	Epileptic fits, herpes zoster, hyperuricaemia, pharyngitis, pneumonia	Arrhythmia, brain tumour and aneurysm, cerebral infarction, delusional condition, epileptic fits, hyperuricaemia, neurosis, psychiatric disease, rheumatoid arthritis, schizophrenia
Time to onset, days; mean ± SD‡	13.8 ± 8.7*	34.9 ± 8.3*
Causative drugs (no. of patients)	Aciclovir (1), amoxicillin (1), bucolome (1), carbamazepine (1), diclofenac (1), minocycline (1), phenobarbital (1), phenytoin (2)	Allopurinol (1), carbamazepine (7), dapsone (1), mexiletine (1), phenobarbital (4), phenytoin (3), salazosulfapyridine (1), zonisamide (1)

DIHS, drug-induced hypersensitivity syndrome; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis. *$P < 0.005$; †not significant; ‡duration between the first drug intake and onset of skin rashes.

SJS/TEN within 4 weeks of discontinuing the causative drug, and no recurrences were seen for several months. By contrast, 18/19 patients with DIHS/DRESS had a slow resolution, requiring approximately 6 weeks, and patients had disease flares for weeks or even months after stopping the drug.

Serum IgG, IgA and IgM levels were significantly lower in patients with DIHS/DRESS than in patients with SJS/TEN: mean ± SD values were 813.2 ± 49.2 mg/dL, 123.5 ± 66.6 mg/dL and 52.6 ± 28.6 mg/dL, respectively for DIHS/DRESS compared with 1256.2 ± 114.4 mg/dL ($P < 0.001$), 262.1 ± 53.1 mg/dL ($P < 0.05$) and 87.9 ± 7.6 mg/dL ($P < 0.05$), respectively, for SJS/TEN. The numbers of circulating white blood cells, lymphocytes and CD3+ T cells were significantly lower in patients with SJS/TEN than in patients with DIHS/DRESS, although most of the results were within the normal ranges (Figs 1a,b). The numbers of CD19+ B cells were less than the normal range in 7/9 patients with DIHS/DRESS and in 5/9 patients with SJS/TEN. The numbers of CD8+ T cells were significantly higher in patients with DIHS/DRESS than in those with SJS/TEN, and the mean value in patients with SJS/TEN was below the normal range (Fig. 1c). By contrast, the numbers of CD56+ natural killer (NK) cells in patients with DIHS/DRESS were lower than in those with SJS/TEN (data not shown), but the difference was not significant. These alterations returned to normal after full recovery in both groups (data not shown).

Mean IFN-γ levels were significantly higher in patients with DIHS/DRESS (105.1 ± 19.1 pg/mL) than in those with SJS/TEN (36.7 ± 14.6 pg/mL) ($P < 0.05$) (Fig. 2). Mean IL-5 levels were also higher in patients with DIHS/DRESS (176.0 ± 93.8 pg/mL) than in those with SJS/TEN (5.4 ± 2.6 pg/mL), but the difference was not significant. By contrast, no significant difference was seen in serum levels of TNF-α, IL-10 (Fig. 2), IL-4 or IL-2 (data not shown) between the two groups. However, there was no significant correlation between these cytokine levels and the severity of symptoms, such as liver dysfunction: nevertheless, high levels of IL-5 were seen in patients with long-term carriage of HCV and HBV regardless of the type of drug eruption. As shown in Fig. 2, the characteristic features of DIHS/DRESS are mainly associated with increased serum levels of IFN-γ.

Patients from both groups were examined for evidence of viral infections. In total, 2/7 examined patients with DIHS/DRESS were positive for anti-HTLV-1 antibodies, and 3/5 examined patients with DIHS/DRESS were positive for anti-HBs antibodies. Epstein–Barr virus (EBV) DNA was detected at onset in peripheral blood samples from 7/9 patients with SJS/TEN and 3/10 with DIHS/DRESS (Table 2). No HIV infection was detected in any of the patients in either group. One patient with SJS who was positive for anti-HCV antibodies also had high levels of serum IgG. High levels of anti-HSV IgG titres (> 70) were detected by enzyme immunoassay in all but 1 patient with SJS/TEN (8/9 patients examined), but only in 3/10 patients with DIHS/DRESS (Fig. 3). Nevertheless, of note, none of the patients with high levels of anti-HSV titres had a known clinical episode of the oral or genital herpes. No relationship was seen between HSV seropositivity and clinical parameters such as serum Ig levels, CD3+ T cell numbers, CD19+ B cell numbers or disease outcome in either group.

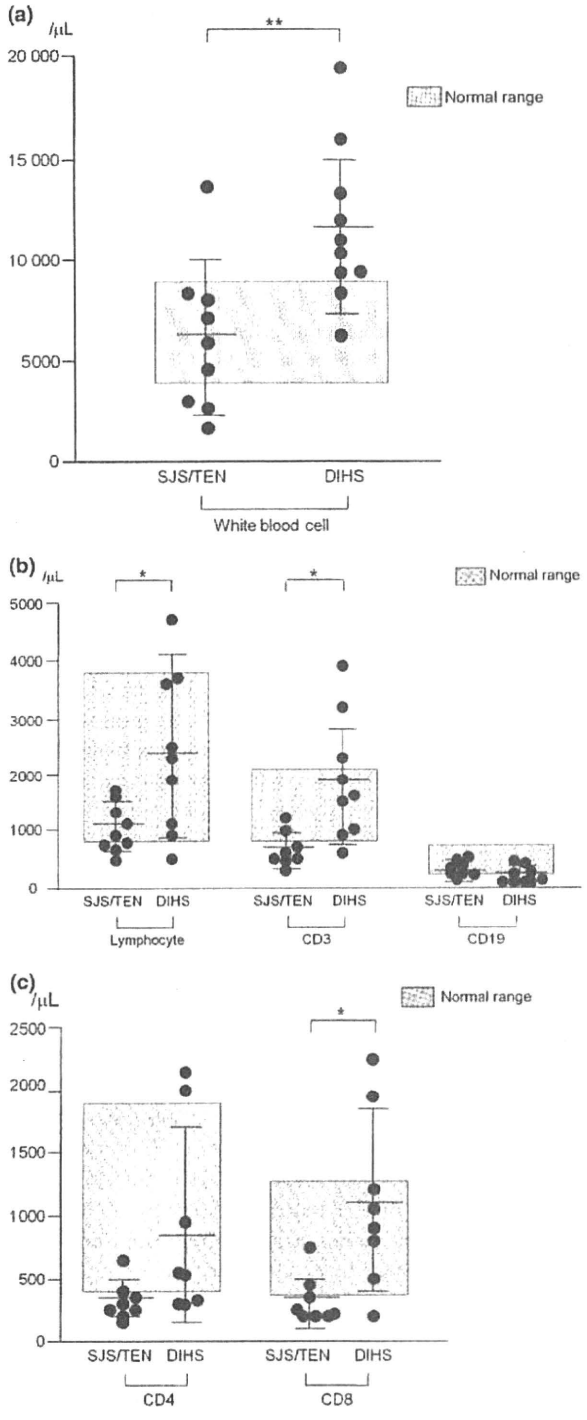

Figure 1 Comparison of circulating cell numbers at onset between Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and drug-induced hypersensitivity syndrome (DIHS). (a) White blood cell; (b) lymphocyte, CD3+ T cell and CD19+ B cell; (c) CD4+ T cell and CD8+ T cell. $^{*}P < 0.05$; $^{**}P < 0.005$.

Discussion

One of the most obvious differences found between these two diseases at time of onset was the imbalance in the composition of circulating T and B cells. In SJS/TEN, a dramatic decrease in circulating T-cell and B-cell numbers was detected, which was associated with a decrease in white blood cell counts; by contrast, in DIHS/DRESS the decrease was confined to the B-cell compartment. In view of the observation that the decline in the number of lymphocytes in SJS/TEN was relatively nonselective with respect to T and B cells, the increased adhesion to endothelial cells and subsequent transendothelial migration into the skin sites due to upregulation of lymphocyte selectin ligands, integrins and chemokine receptors seen in SJS/TEN[18] may be the cause of the decrease in the number of T and B cells in blood. Thus, the decline in lymphocyte numbers in SJS/TEN may reflect their accumulation in the inflamed skin sites.

By contrast, increased tissue migration probably does not explain the decreased B-cell proportion in DIHS/DRESS. Considering that a profound decrease in serum Ig levels was also seen at the time of DIHS/DRESS onset and that B cells were rarely detected in the skin lesions (unpublished observations), a gradual loss in B-cell numbers should have occurred through preferential cell death long before the onset of clinical symptoms. We propose that this loss in the B cells and possibly NK cells, together with a dramatic decrease in serum immunoglobulin levels, is likely to be the basis for the subsequent reactivation of HHV-6 and other herpesviruses that has been reported to occur in patients with DIHS/DRESS.[4,10]

Our cytokine data in patients with DIHS/DRESS are consistent with previous reports showing increased IFN-γ and IL-5 production.[19] Such patterns did not result from differences in therapeutic regimens, because most of the patients had not received prednisolone before sampling (only one patient in each group had been treated before sampling). In most cases of DIHS/DRESS, serum levels of IFN-γ, TNF-α and IL-5 were related to those of IL-10, suggesting that the increase in IL-10 production results from the overproduction of these proinflammatory cytokines and IL-5. These results indicate that increased production of IL-10 could reflect an appropriate response that serves to limit the pathogenic effects of these proinflammatory cytokines.

Another important factor that influences the pathological phenotype is the presence of underlying viral infections. In addition to the subsequent occurrence of sequential reactivations of herpesviruses exclusively detected during the course of DIHS/DRESS,[4,9] persistent