Letter

Mice lacking functional EGFR have thin and immature skin. In addition, inhibition of EGFR signaling in basal keratinocytes leads to growth abnormalities and epidermal detachment (4). Since acneiform papules result from skin fragility due to inhibition of EGFR (5), these papules may occur not only on seborrheic areas but also on areas of minor pressure and shear. Finally, these papules or pustules may develop into pressure sore-like ulcers because of the skin's fragility. In other words, pressure sore-like ulcers are a kind of Koebner phenomenon associated with EGFR inhibitors.

On initiation of anti-EGFR therapy, skin care to reduce skin toxicity, such as the use of emollient cream and staying out of the sun, has been recommended. However, management to avoid pressure sore-like ulcers has not been proposed before. Therefore, we argue for the need for preventive management to reduce pressure sore-like ulcers when starting EGFR inhibitor therapy. Management options include repositioning, use of higher-specification foam mattresses and seat cushions, and limiting the length of time spent sitting in a chair without pressure relief.

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◆特集／初歩から学べる皮膚科検査の実際

重症薬疹（DIHS，SJS，TEN）の検査

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Key words：Stevens-Johnson 症候群（Stevens-Johnson syndrome），中毒性表皮壊死症（toxic epidermal necrolysis），薬剤性過敏症症候群（drug-induced hypersensitivity syndrome），バイタルサイン（vital sign），迅速皮膚生検（rapid frozen-section diagnosis）

Abstract　重症薬疹の診療においては，早期に診断し治療を始めること，治療薬の初期量を決定すること，経過中に適切に生じてくるさまざまな病態を把握することが求められる．病型に応じて必要な検査は異なってくる．SJS/TEN は，皮膚粘膜の障害により定義される疾患であり，早期診断のツールとして迅速皮膚病理診断が有用である．また，病状把握のために眼の検査も欠かすことができない．治療開始後，特に TEN では，全身状態が刻々と変化し感染症への対策が重要となってくるため，バイタルサインに注意し，感染症の診断のための検査が大切となる．一方，DIHS は徐々に症状がそろってくる疾患であり，当初は臓器障害がなくても，薬剤中止後の増悪がみられるならば，血液検査やリンパ節の触診により経過をみる．DIHS と判断されれば，さらにその後はウイルスの検査を行っていく必要がある．

はじめに

通常の薬疹治療の基本は原因薬剤の中止であり，ほとんどは特別な治療を行わなくても軽快するが，重症薬疹は死亡したり後遺症を残したりすることがある疾患で，適切な治療が求められる．早期に診断し治療を始めること，治療薬の初期量を決定すること，経過中に適切に生じてくるさまざまな病態を把握することが，重症薬疹の診療において求められ，そのための検査を行う必要がある．

本稿では，重症薬疹のうち Stevens-Johnson 症候群（SJS），中毒性表皮壊死症（TEN），薬剤性過敏症症候群（DIHS）検査について解説する．SJS と TEN は重篤な皮膚粘膜障害を特徴とする疾患，DIHS は皮膚障害に加えて多臓器障害をきたす疾患であり，SJS と TEN はまとめて記載している．

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Stevens-Johnson 症候群（SJS）／中毒性表皮壊死症（TEN）

1．早期診断のための検査

これら疾患は，粘膜上皮障害や表皮障害をもって診断される疾患であるため，確定のためには皮膚生検が必須である．通常の皮膚生検では検査結果が出るまで 1 週間前後を要し早期診断には向かないため，迅速皮膚病理診断法を用いる[1]．

具体的には，通常の標本用の皮膚とは別に採取した皮膚組織を OCT compound などにより包埋し，液体窒素で急速冷凍を行う．標本はクライオスタットで薄切してホルマリン加メタノールなどで固定し，HE 染色を行う．悪性腫瘍の術中迅速診断と同じ方法であり，特別な技術を要する検査ではない．2009 年に行われた重症薬疹研究班における SJS/TEN の疫学調査においても，それぞれ 8～9％の症例が迅速病理診断検査による診断を受けている[2]．

表皮の全層性壊死が SJS/TEN の重要な所見と

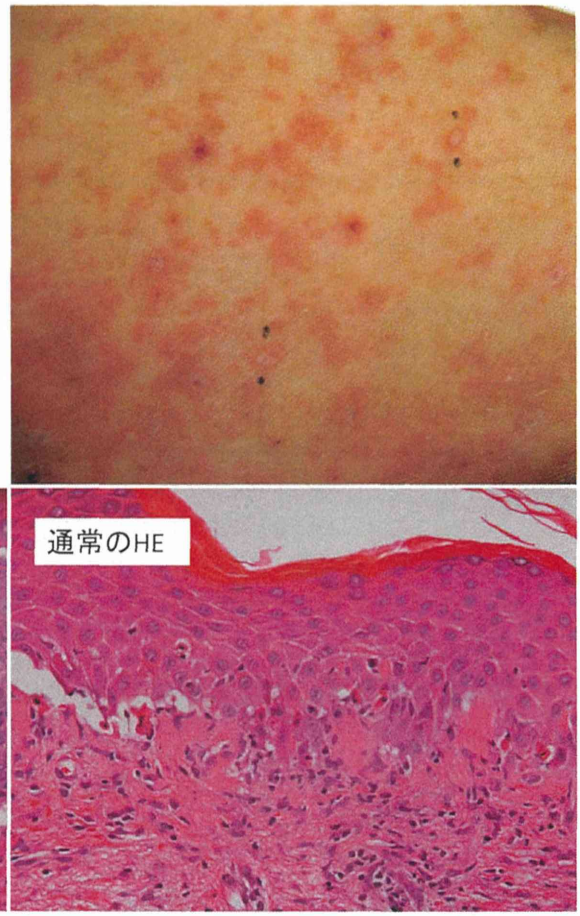

図 1.
TEN の迅速病理診断
水疱部分を 2 か所生検した．表皮下に水疱を形成し，基底層を中心とした表皮角化細胞の変性壊死を認める．凍結皮膚の迅速 HE 染色でも通常の HE 染色と比較して遜色のない所見をえることができる．

いわれているが，前述の疫学調査委によると，診断時に全層性壊死が確認されたのは TEN では 74%，SJS では 24%である[2]．病変皮膚の採取時期により病理組織像は異なると思われ，全層性壊死でなくても，表皮角化細胞のアポトーシス，液状変性，表皮下水疱の形成などにより表皮障害があれば診断可能である．これらの所見は，迅速病理標本でも十分みてとれる(図 1)．

2．重症度を判断するための検査

a）眼の検査

SJS/TEN の眼の後遺症はよく知られており，なんらかの後遺症がそれぞれ 79%，66%にみられる[2]．そのため，眼の重症度の判定と早期からの適切な治療介入が求められる．口腔粘膜や皮膚障害の重症度は視診で判断できるが，眼の障害の程度を皮膚科医が視診のみで判断することは危険である．充血が強く痛みの訴えがあるときには必ず眼科医の診察を仰ぎ，専門的検査を受けることが大切である．眼脂を認めるときには，細菌培養を行うことが望ましい[3]．眼にステロイド外用剤や点眼を用いて治療を行うに当たって必要な情報であり，ブドウ球菌性熱傷様皮膚症候群の鑑別が問題となる場合にも必要な検査である．

b）バイタルサイン

基本的なことであるが，血圧，脈拍数，呼吸数，体温などのバイタルサインの確認を行う．TEN では，SCORTEN (severity-of-illness score for TEN)という重症度判定があり[4]，入院時の年齢，皮膚の障害範囲，バイタルサイン，血液検査結果などを合わせて評価する(表 1)．それぞれの項目を 1 点として計算して合計点数で判断し，点数が高いほど死亡の危険性が高くなる(表 2)．血液ガスを測定しない場合には血中の重炭酸塩($HCO3^-$)は判定できないが，たとえこの項目を除いても参考にはなりうる．

3．病状を把握するための検査

a）一般血液検査

ときに白血球減少や顆粒球減少がみられ，肝・

表 1. SCORTEN(severity-of-illness score for TEN)
(文献4より引用，一部改変)

SCORTEN	
年齢	40歳以上
悪性腫瘍の合併	あり
脈拍	120回/分以上
入院時の体表面積における表皮剝離面積	10%以上
血清 BUN 値	27 mg/dl 以上
$HCO3^-$値	20 mEq/l 未満
血糖値	250 mg/dl 以上

それぞれの項目に該当すると1点を算定する．合計が0～7点となり，合計点により重症度を判定する．

腎機能障害はSJS/TENの7割程度にみられる[2]．

b）画像診断

細気管支炎を合併すると重篤な経過をとる．呼吸器症状を認めるときには，胸部X線撮影やCT検査，血液ガス検査を行う．

c）感染症の検査

薬剤性により生じていると考えられても，マイコプラズマ感染がベースに存在していることがあり，抗体価を検討する．単純ヘルペス感染症に伴う多形紅斑は鑑別診断として挙げられる．また，SJS/TENでは治療に用いるステロイド薬の影響もあり易感染性となるため，それぞれ75%，90%にさまざまな感染症を合併し，しばしば死亡の原因となりうる．皮膚のびらん面に感染が疑われるときには細菌培養を提出する．また，バイタルサインの変化に留意し，必要に応じて血液，咽頭，喀痰，カテーテル，尿から細菌培養を適宜行う．敗血症を生じると，プロカルシトニンの上昇がCRPの上昇に先行してみられ，早期診断に役立つ．また，サイトメガロウイルス感染症，ニューモシスチス肺炎，真菌性肺炎なども生じうる[2]．

4．HLA検査

SJS/TENにおいて，カルバマゼピンではHLA-B*1511[5]，アロプリノールではHLA-B*5801[6]のHLAを有することが日本人におけるリスクファクターとして知られている．

5．原因薬剤の検索

SJS/TENでは，DLST検査を早期に検討することが有用であると報告されている[7]．発症後1週間以内の急性期に陽性率が最も高く，ステロイド薬投与の影響はほとんどないといわれている[6]．

表 2. SCORTENにより予想される死亡率
(文献4より引用，一部改変)

SCORTEN	予想される死亡率(%)
0～1	3.2
2	12.1
3	35.5
4	58.3
5以上	90.0

薬剤性過敏症症候群(DIHS)

1．早期診断のための検査

a）血液検査

DIHSは発熱，皮疹と他臓器障害を特徴とする薬疹であり，血液像，肝機能，腎機能を検討することが必要である．DIHSでは原因薬剤中止後に多臓器障害が徐々にそろってくることも多いため，発熱が続き皮疹の増悪がみられるときには，初診時に検査値に問題がなくても，その後，血液検査(末梢血液像，肝機能，腎機能)を数日おきに行う．

DIHSへ発展するかどうかの指標となりうる検査として，一つはIgGの低値がある．また，保険適応外であるが，可溶性IL-2レセプターやTARCの高値もDIHSの指標となる可能性がある(未発表データおよび文献8より)．

b）リンパ節の触診

リンパ節腫脹はDIHSの診断基準の項目の一つであるが，初診時からはみられず徐々に出現してくることもある．当初は触知しなくても，皮疹の増悪が続く間は毎日みておく必要がある．

c）皮膚生検

DIHSでは，真皮内のリンパ球浸潤が強いことが多い．また，稀ではあるが初期の皮疹，ときには経過中に再燃した皮膚症状が中毒性表皮壊死症となることがある．皮膚病理診断が可能であれば，SJS/TEN治療のガイドラインに準じた速やかな治療の開始が可能である．

2．病状を把握するための検査

a）バイタルサイン

初診時の重篤感はバイタルサインでとらえるこ

とができ，治療開始後に生じる感染症や合併症の全身状態の把握にも，バイタルサインは重要である．

b）ウイルスの検査

DIHSでみられるウイルスの再活性化は病態に関与してくることがあり，経過中に症状の再燃や新たな病態が出現したときにはウイルスの関与が疑われる．HHV-6の再活性化はDIHSの診断において重要な意味を持ち，サイトメガロウイルスはDIHSの治療に当たって重要である．

(1) HHV-6の検査

治療開始後いったん軽快したあとの1回目の発熱，肝障害の再燃は，HHV-6の再活性化によることが多い．通常，DIHSの発症後10日目以降，1か月以内に認められる．

このエピソードの前後で血清抗体価の変動をみると，HHV-6 IgG抗体価の上昇が確認できる(保険診療外)．発熱のみられている間の血清中にはHHV-6 DNAが検出される．通常状態では血清にHHV-6 DNAは検出されないため，検出されたときには再活性化が生じていると判断できる．また，全血でHHV-6 DNAを検討する場合には，DNA量の増減を確認する必要がある．潜伏感染を検出している可能性があり，一度だけの検査で陽性であった場合には評価はできない．中枢神経障害が生じた場合は，髄液からのHHV-6 DNAの検出を検討する．

(2) サイトメガロウイルスの検査

HHV-6の後には，サイトメガロウイルスの再活性化を生じ，感染症にまで発展する場合がある．治療開始時にサイトメガロウイルス抗体価を測定し，既感染か未感染か判断しておくことは，その後の経過観察に有用な情報となる．サイトメガロウイルス感染症の症状は，発熱，消化管障害(下痢，消化管出血，穿孔など)，肝障害，肺炎，皮膚潰瘍などさまざまである[9]．

HHV-6の再活性化が終わった後，ステロイド薬の速やかな減量や中止ができない場合にはサイトメガロウイルスの再活性化の有無を定期的に検討する．ただ，発症時から[10]，あるいはHHV-6再活性化と同じころに既にサイトメガロウイルスの再活性化がみられる症例もある[11]．サイトメガロウイルスの再活性化の判定に抗体価検査は有用でなく，抗原血症検査が推奨されている．しかし，消化管のサイトメガロウイルス感染では抗原血症の陽性率が低いことが知られている．そのため，消化管の障害があるときには，内視鏡検査で生検を行い，病理組織学的検討を行うことが勧められる．皮膚潰瘍についても，生検を行い，サイトメガロウイルス抗原の発現の有無を免疫染色で確認することが必要である．

抗原血症陽性，全血中のサイトメガロウイルスDNA陽性は，再活性化があることの証明になるが，感染症の存在を示しているのではない．臨床症状を伴っておらず，抗原血症の値が低い場合には，定期的に経過をみることで陰性化することがある．臨床症状を伴いウイルスの関与が否定できないときや，検査値が高値であるときには，治療が必要となる．

c）その他感染症の検査

DIHSはウイルスの再活性化しやすい免疫抑制状態があり，さらに治療に用いるステロイド薬による免疫抑制も重なるため，日和見感染や重篤な細菌感染症も生じうる．発熱とともにプロカルシトニンやCRPの上昇があれば細菌感染の合併を考え，血液培養や適宜画像診断を考慮する．ステロイド薬の投与が長期にわたるときには，血中β-D-グルカン値も検討し，ニューモシスチス肺炎の発症に注意する．

3．DIHSにみられる合併症の検査

DIHSの発症後にみられる合併症として，甲状腺機能異常症，1型糖尿病，劇症1型糖尿病，その他自己免疫性疾患がある．定期的に検査を行う必要はないと考えているが，疑わしい症状が出現した際には検査を行う．

4．HLA検査

DIHS特有といえるHLAの異常は見つかっていないが，カルバマゼピンによる薬疹ではHLA-

表 3. SJS/TEN に行う検査(愛媛大学皮膚科の場合)

初診時(入院時)	入院中定期的に行う検査	入院中に適宜行う検査
皮膚生検(迅速 HE，通常の HE)		
バイタルサイン 血圧，脈拍数，呼吸数，体温	**バイタルサイン**	
血液検査 一般血液検査(末梢血液像，肝機能，腎機能，電解質，血糖，HbA1c，CRP など) 定性 TPHA，定性 RPR HBs 抗原，HBc 抗体，HCV 抗体(HIV 抗体) マイコプラズマ抗体 単純ヘルペス抗体(SJS の場合) サイトメガロウイルス抗体(感染既往の評価のため)	**血液検査** 一般血液検査 サイトメガロウイルス抗原血症(2 週に 1 回程度) β-D グルカン(2 週に 1 回程度)	**血液検査** マイコプラズマ抗体(抗体価上昇確認が必要な場合) 単純ヘルペス抗体(抗体価上昇確認が必要な場合) プロカルシトニン(敗血症疑いのとき)
DLST		
(血液ガス)		
検尿		
画像検査(胸部 X 線撮影，必要なら CT)		**画像検査**
心電図		
眼科受診	**(眼科検査)**	
細菌培養(皮膚，眼脂など)		**細菌培養**(血液，喀痰，咽頭，カテーテル，尿など)
		その他 HLA DNA typing(HLA-A or HLA-B)

注) 保険適応外検査を含む

A*3101[12]，アロプリノールによる重症薬疹は HLA-B*5801 の関与がみられる．また，DIHS に発症する劇症 1 型糖尿病では HLA-B*62 との関連性が報告されており[13]，陽性であるときには注意が必要と考えている．

5．原因薬剤の検索

SJS/TEN と異なり，DIHS では発症早期の DLST の陽性率が低く，1 か月目以降のほうが陽性結果を得やすい[6]．また，薬剤によるがパッチテストの陽性率も比較的高い．

おわりに

重症薬疹の検査は多岐にわたり，また，特殊な検査も多い．地域性もあるが，遭遇する頻度がそれほど高い疾患ではないため，とっさに必要な検査をもれなく行うことが難しい．愛媛大学皮膚科で行っている検査を表 3，4 に挙げた．参考になれば幸いである．

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表 4. DIHS に行う検査(愛媛大学皮膚科の場合)

初診時(入院時)	入院中定期的に行う検査	入院中，退院後に適宜行う検査
皮膚生検(通常の HE，必要なら迅速 HE)		**皮膚生検**(皮疹に変化がある場合)
バイタルサイン(血圧，脈拍数，呼吸数，体温)	**バイタルサイン**	
リンパ節の触診	**リンパ節の触診**(発症後 2~3 週まで)	
血液検査 一般血液検査(末梢血液像，肝機能，腎機能，電解質，血糖，HbA1c，CRP など) 定性 TPHA，定性 RPR HBs 抗原，HBc 抗体，HCV 抗体(HIV 抗体) HHV-6 IgG 抗体 サイトメガロウイルス IgG，IgM 抗体(感染既往の評価のため) EBV 抗体(EBNA，VCA IgM，VCA IgG) IgG，IgA，IgM，IgE sIL-2R TARC (血清，全血は保存しておく)	**血液検査** 一般血液検査(週に 1~2 回) サイトメガロウイルス抗原血症(2 週に 1 回程度) β-D グルカン(2 週に 1 回程度) sIL-2R(2 週に 1 回程度) (血清，全血は週に 1，2 回保存する) ↓ HHV-6，サイトメガロウイルス，EBV の DNA 検査	**血液検査** HHV-6 IgG 抗体(再活性化後あるいは発症 1 か月目以降) サイトメガロウイルス IgG，IgM 抗体(再活性化の後) EBV 抗体 DLST(発症後 1 か月目以降) IgG，IgA，IgE プロカルシトニン(敗血症を疑うとき)
検尿		
画像検査(胸部 X 線撮影，必要なら CT)		**画像検査**
心電図		**細菌培養**(血液，尿など)
その他 HLA DNA typing(HLA-B62 を含む)(HLA-A or/and HLA-B)		**その他** 薬剤パッチテスト 甲状腺，1 型糖尿病自己抗体，膠原病などの検査

注) 保険適応外検査を含む

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depigmentation. Moreover, evaluation is desirable for the possibility of hair depigmentation being a hallmark of efficacy of TKI.

CONFLICT OF INTEREST: The authors have no conflict of interest to declare.

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Pazopanib-induced leg ulcer in a patient with malignant fibrous histiocytoma

Dear Editor,

Pazopanib is an oral, multi-targeted, tyrosine kinase inhibitor that has recently been approved for advanced soft tissue sarcoma. We herein report a patient with malignant fibrous histiocytoma treated with pazopanib who developed severe leg ulcers without progression of lung metastasis.

An 84-year-old Japanese woman noticed a red nodule on her right forearm and visited a clinic in March 2012. Histopathological findings of the skin biopsy specimen were suggestive of soft tissue sarcoma and she was referred to our hospital. A firm, immobile, red tumor measuring 45 mm × 35 mm in diameter was noted (Fig. 1a). Additional radiological examinations revealed no metastasis. Surgical local excision was performed and positive deep margins were evident histologically. Atypical spindle cells with bizarre nuclei increased in vague intricate pattern. Immunohistochemical results were not positive for S-100, CD34, CD68, smooth muscle actin or desmin. Therefore, diagnosis was pleomorphic malignant fibrous histiocytoma with pT1aN0M0 (stage IA). Five months later, the red nodule recurred at the same site, and computed tomography revealed a new nodule in the right lung suggestive of distant metastasis. Surgical excision again revealed positive deep margins. She declined to undergo radiotherapy, multi-agent chemotherapy as an inpatient or radical excision that might have resulted in dysfunction because of her advanced age and dementia. We therefore started pazopanib (800 mg) on an outpatient basis. Because of serious adverse reactions (grade 3), such as hypertension, fatigue and anorexia, pazopanib was immediately discontinued. After the patient completely recovered from these adverse events, pazopanib was restarted at 400 mg. However, small skin erosions developed on both lower legs that were associated with stasis dermatitis (Fig. 1b), and severe leg ulcers developed 2 weeks after the second administration of pazopanib (Fig. 1c). Ultrasonogram, enhanced computed tomography and laboratory data ruled out the thrombosis and

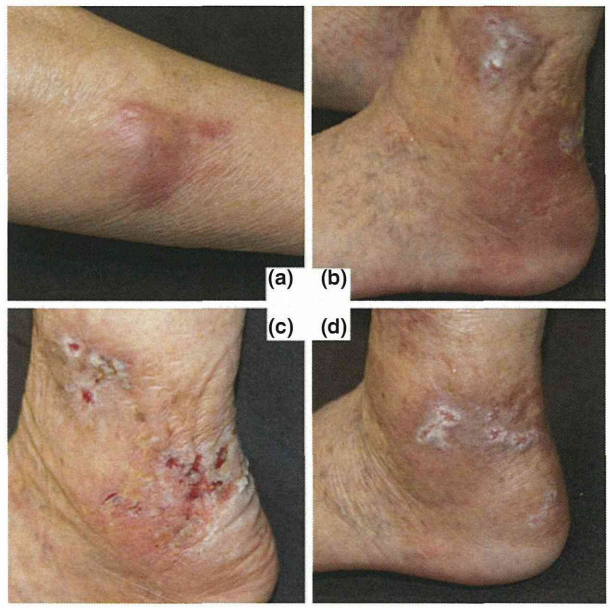

Figure 1. Clinical appearance of (a) a tumor on the right forearm at the first visit, (b) the skin ulcers on the left lower leg before the second pazopanib treatment, (c) 2 weeks after treatment with pazopanib 400 mg and (d) 8 weeks after cessation of pazopanib.

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drug/cancer-associated vasculitis. Pazopanib was promptly discontinued again. The ulcers were treated with alprostadil-alfadex ointment and povidone-iodine sugar ointment, but did not respond to these treatments and persisted for more than 3 months after cessation of pazopanib. No progression of lung metastasis was observed more than 1 year after the second operation (Fig. 1d).

Pazopanib is a novel small molecule inhibitor such as vascular endothelial growth factor receptor. It has shown broad antitumor activity in various types of human tumor xenografts in mice *in vivo*.[1] Moreover, in the PALETTE study, a randomized, double-blinded, placebo-controlled phase 3 trial for patients with metastatic non-adipocytic soft tissue sarcoma after failure of standard chemotherapy, progression-free survival was prolonged in the pazopanib group compared with the placebo group.[2] Several trials of pazopanib are ongoing not only for soft tissue sarcoma but also for other malignant neoplasms, with expectations of an antiangiogenic effect.[3–5] The present case clearly showed the antiangiogenic effect of pazopanib. Although our patient initially had some atrophie blanche due to stasis dermatitis, exacerbation of the leg ulcers occurred soon after pazopanib therapy. Taken together, the persistence of skin ulcers and lack of progression of the lung metastasis despite cessation of pazopanib suggested that pazopanib has a potential therapeutic effect on malignant neoplasms.

CONFLICT OF INTEREST: The authors have no conflict of interest.

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Pigmented epithelioid melanocytoma with lymph node metastasis in a patient with uncontrolled atopic dermatitis

Dear Editor,

We experienced a case of pigmented epithelioid melanocytoma (PEM) of the skin and lymph nodes accompanied by poorly controlled atopic dermatitis. A 15-year-old Japanese female had suffered from atopic dermatitis since childhood. Her parents had noticed a black and well-defined rough plaque measuring 20 mm in diameter on the right patella after birth. No personal or family history of Carney complex was present. At the first hospitalization, an erosive dome-shaped black nodule with an irregular cobblestone surface growing up to 30 mm × 40 mm and a neighboring small black papule were detected above the lichenified lesion on the right patella (Fig. 1a). Computed tomography showed significant swelling of the inguinal lymph nodes of more than 20 mm, suggesting lymph node metastasis; therefore, we simultaneously resected the skin tumors and black sentinel lymph nodes. A small skin lesion was diagnosed as a cellular blue nevus. On the other hand, a larger lesion contained mild-to-moderate atypical melanocytic cells proliferating throughout the basal layer of the acanthotic epidermis with heavy melanin deposition. In contrast, the tumor cells in the mid-to-deep dermis were uniform in size and ellipsoidal in shape (Fig. 1b–d). The black and elastic soft inguinal lymph nodes (Fig. 1e) contained a number of ellipsoidal pigmented cells positive for Melan-A in the subcapsular and trabecular regions (Fig. 1f–h). The MIB-1 index of the tumor cells was less than 10% at both sites and, taken together, we concluded a diagnosis of PEM and its metastasis to a draining lymph node. The patient has since fared well, without any evidence of recurrence or metastasis, for 4 years after the initial resection.

Pigmented epithelioid melanocytoma was originally described in 2004 and is conceptually classified as a heavily pigmented low-grade melanocytic tumor with metastatic potential.[1] PEM usually presents as a slowly growing darkly pigmented dermal nodule and mostly shows a better prognosis compared with malignant pigmented tumors.[1] Detailed histological comparison and differentiation of PEM with malignant blue nevus and atypical cellular blue nevus also lead to a cor-

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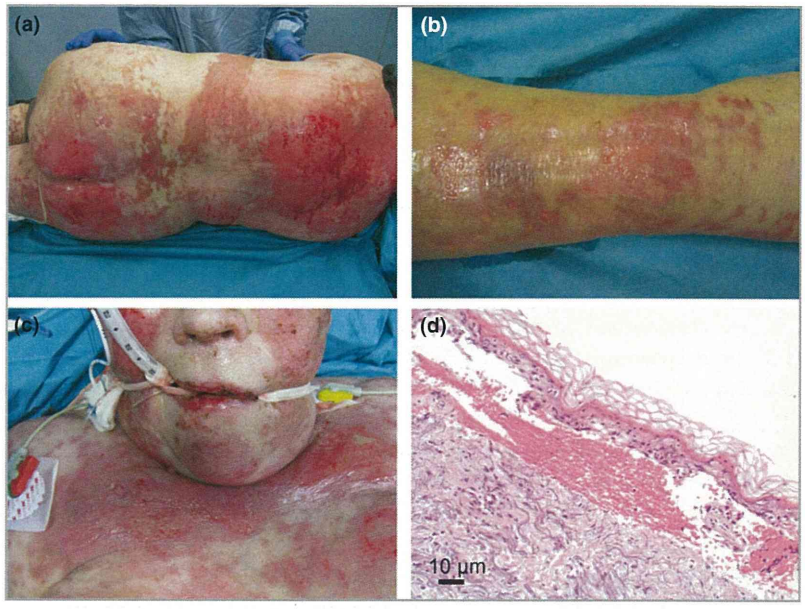

Fig 2. Photographs of skin manifestations in patient 2 following wound debridement, showing (a) the patient's back and (b) a lower leg with multiple macules, papules, blisters and erythematous and epidermolytic areas, typical of toxic epidermal necrolysis (TEN). (c) Involvement of the inner lip mucosa in this patient. (d) Haematoxylin and eosin-stained sections of a skin biopsy specimen of patient 2, with typical epidermolysis and leucocyte infiltrate of TEN.

taking herbal preparations in capsules, an imaginable common denominator of TEN development.

A single or multiplier effect by idiosyncratic, dose-related or drug-interactive reactions of phytochemicals or contaminants might be involved in the development of TEN in these patients. The objective evaluation by the Naranjo adverse drug reaction (ADR) probability scale[9] calculated a possible ADR by the herbal remedy in cases 1 and 3 and a probable cause in case 2. In all cases, the TEN-specific algorithm for epidermal necrolysis (ALDEN) confirmed a possible cause of herbal remedies in TEN developement.[10]

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The serum level of HMGB1 (high mobility group box 1 protein) is preferentially high in drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms

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Dear Editor, Drug-induced hypersensitivity syndrome (DIHS), also known as drug reaction with eosinophilia and systemic symptoms (DRESS), is characterized by high fever, multiple

organ involvement and haematological disorders, essentially without severe erythema or epidermal apoptosis.[1] Sequential reactivation of human herpes virus (HHV)-6 is deeply involved in the pathophysiology and persistence of DIHS/DRESS. A preceding increase in proinflammatory cytokines such as interleukin (IL)-6 and tumour necrosis factor (TNF)-α seems to be relevant to the viral reactivation in DIHS/DRESS, while the exact mechanism is still unclear.[2]

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), other severe cutaneous adverse drug reactions (cADRs), are characterized by high fever, severe erythema and widespread epidermal damage due to keratinocyte apoptosis. Activated cytotoxic T cells and natural killer cells are involved in SJS/TEN.[3] The molecular cytotoxicity of Fas and cytotoxic proteins, including perforin/granzyme B and granulysin, are thought to contribute to induction of keratinocyte apoptosis.[3] High mobility group box 1 protein (HMGB1) is a nonhistone nuclear protein that is released from severely damaged cells. HMGB1 plays a role in transcriptional regulation in the nucleus, while outside of the cell it serves as an activator of the inflammatory cascade.[4] It was recently reported that HMGB1 levels are increased during the acute stage of SJS/TEN and can serve as an early diagnostic marker for SJS/TEN.[5] However, the level of HMGB1 at the onset of other severe cADRs such as DIHS/DRESS has not been investigated. In addition, although there are limited reports on serum cytokine levels in cADRs,[6] these cytokines have not been analysed with regards to HMGB1, which may induce aberrant cytokine production. To clarify the relationship between aberrant HMGB1 and cytokine production at disease onset, and the clinical manifestations elicited, we investigated serum HMGB1 and cytokine profiles in various cADRs.

Peripheral blood was taken from healthy controls and patients with various types of cADR including maculopapular (MP) type, erythema multiforme (EM), SJS, TEN and DIHS/DRESS at the time of onset and recovery. Onset is an acute exacerbation phase (< 7 days) and recovery is a remission phase of cADRs. Serum was stored at −80 °C and cytokine levels were measured by luminometric bead array using the Bio-Plex Suspension Array System (BioRad, Hemel Hempstead, U.K.). HMGB1 was measured by enzyme-linked immunosorbent assay. The groups consisted of the following subjects (full details in Table 1): healthy controls, 14 cases; MP/EM, 11 cases; SJS/TEN, 17 cases and DIHS/DRESS, 17 cases. For comparison of cytokine levels between healthy controls and each cADR group at onset, and between onset and recovery in each cADR group, the Mann–Whitney test and Wilcoxon matched-pairs tests were used, respectively. Statistical significance was established at $P < 0{\cdot}05$ and $P < 0{\cdot}01$.

Table 1 Profile of each group

Group	Number	Age (years), mean ± SD	Sex, n (male/female)	Type
Healthy controls	14	53·1 ± 15·3	8/6	–
MP/EM	11	65·3 ± 8·9	6/5	MP 6/EM 5
SJS/TEN	17	56·5 ± 19·1	7/10	SJS 13/TEN 4
DIHS/DRESS	17	53·5 ± 14·0	10/7	Typical 13/atypical 4[a]

MP, maculopapular; EM, erythema multiforme; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms. [a]Typical, with reactivation of human herpesvirus (HHV)-6; atypical, without reactivation of HHV-6.

HMGB1 was high in both SJS/TEN and DIHS/DRESS compared with healthy controls and other cADRs, but the level was significantly higher in DIHS/DRESS than in SJS/TEN. Comparison of cytokine levels between SJS/TEN and DIHS/DRESS revealed a prominent increase in T helper (Th)2 cytokines/chemokines such as IL-5, IL-9 and IL-13 in DIHS/DRESS. Additionally, IL-10 (an anti-inflammatory cytokine) and IL-12 were elevated in DIHS/DRESS (Fig. 1a). Concerning the serum cytokine levels at the time of onset in each group, the following were significantly increased compared with healthy controls: IL-5, IL-6, chemokine (C-X-C) motif ligand (CXCL)-8, IL-9, IL-12, eotaxin, granulocyte macrophage colony-stimulating factor (GM-CSF), CXCL-10 and vascular endothelial growth factor (VEGF) in MP/EM; IL-6, IL-12 and CXCL-10 in SJS/TEN; and IL-5, IL-6, IL-9, IL-10, IL-12, IL-13, IL-15, eotaxin, GM-CSF, interferon (IFN)-γ, CXCL-10 and VEGF in DIHS/DRESS. Proinflammatory cytokines such as TNF-α and IFN-γ were not necessarily high in severe cADRs. Most, but not all, cytokines returned to normal levels with treatment at the time of recovery (Fig. 1).

Although the levels of various types of serum cytokines were elevated at cADR onset, the levels of proinflammatory cytokines did not correlate with the types of cADR or disease severity. These results suggest that the overproduction of these cytokines contributes to promoting inflammation, but that mechanisms other than an increase of proinflammatory cytokines are essential for inducing the massive keratinocyte apoptosis observed in SJS/TEN.

In DIHS/DRESS, Th2 cytokines, HMGB1 and IL-10, were increased. Recent studies have reported that not only Th2 cytokines, but also Th2 chemokines such as thymus and activation-regulated chemokine, were elevated in serum in DIHS/DRESS.[6,7] In addition, HMGB1 was more highly elevated than in SJS/TEN. HMGB1 has been shown to induce the differentiation of dendritic cells (DCs) to $CD11c^{low}CD45RB^{high}$ DCs followed by shifting of Th1 to Th2 *in vitro*.[8] Furthermore, high expression of HMGB1 in DIHS/DRESS skin has been reported.[9] The area of expression of HMGB1 was larger in DIHS/DRESS lesions than in SJS lesions regardless of keratinocyte damage. Translocation of HMGB1 occurred in DIHS epidermal cells, and this HMGB1 attracted monomyeloid precursors harbouring HHV-6, resulting in HHV-6 transmission to skin-infiltrating $CD4^+$ T cells, which is essential for HHV-6 replication in DIHS/DRESS. On the other hand, IL-10, which is an anti-inflammatory cytokine, was also highly elevated in DIHS/DRESS. It has been reported that expansion of $Foxp3^+CD25^+$ T regulatory cells (Tregs) was observed

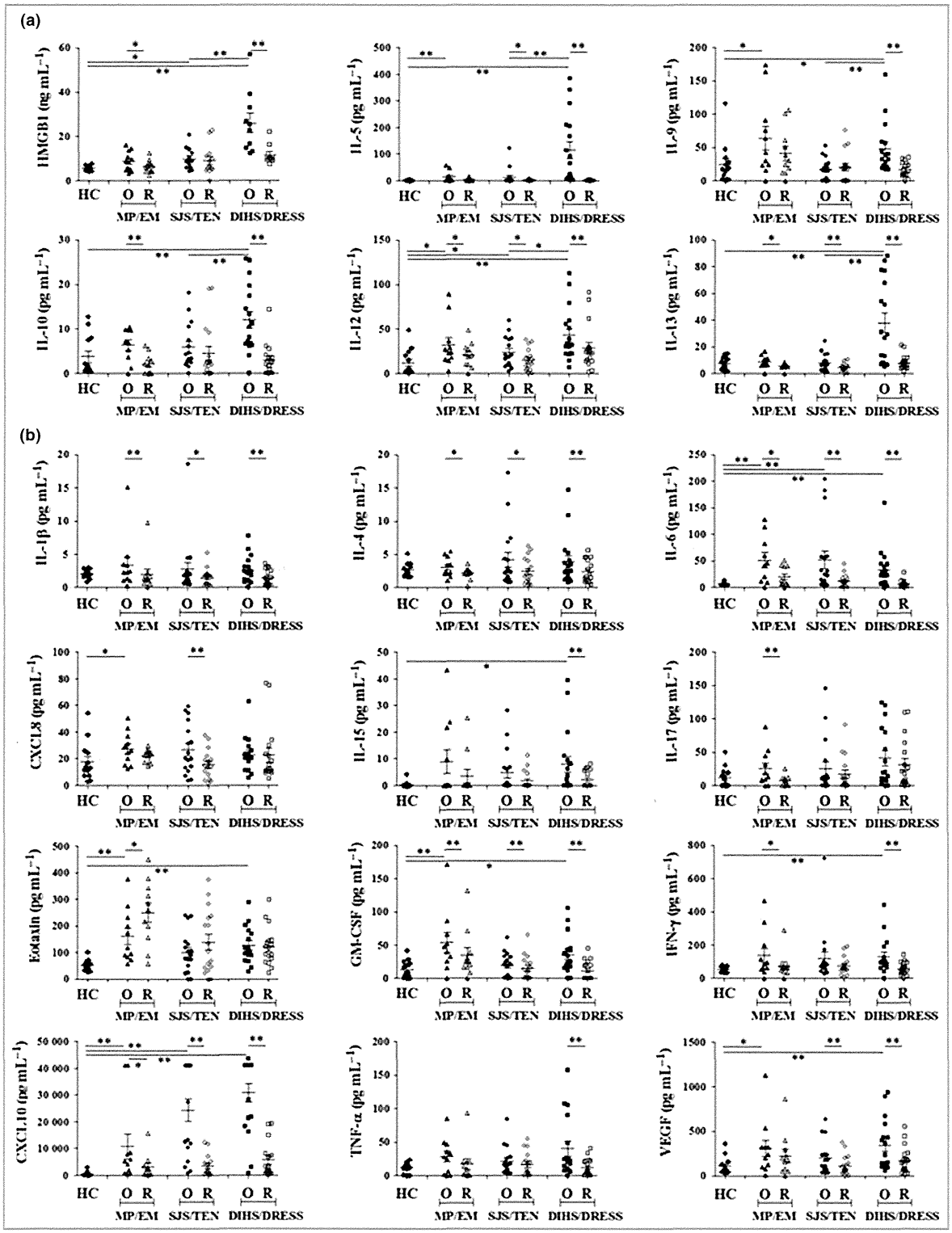

Fig 1. Serum high mobility group box 1 protein (HMGB1) and cytokine levels were analysed by enzyme-linked immunosorbent assay and luminometric bead array. To compare cytokine levels between healthy controls (HC) and each cutaneous adverse drug reaction (cADR) group at onset and between onset and recovery in each cADR group, the Mann–Whitney test and Wilcoxon matched-pairs tests were used, respectively. Significantly higher levels of (a) cytokines and (b) other proinflammatory cytokines in drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) than in Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN). CXCL, chemokine (C-X-C) motif ligand; EM, erythema multiforme; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; MP, maculopapular; O, onset of disease; R, recovery from disease; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor. *$P < 0{\cdot}05$, **$P < 0{\cdot}01$.

during the acute stage of DIHS but not of TEN, whereas Tregs decrease dramatically in the late stage of DIHS.[10] Taken together, HMGB1 released during the acute phase of DIHS/DRESS might facilitate Th2 cell activation induced by the causative drug, resulting in exacerbation. In this context, Th2 cells and Tregs, both producing IL-10, along with other activated cells producing proinflammatory cytokines, characterize the pathophysiology of DIHS/DRESS in the early stage.

In conclusion, cytokine storm occurs in various types of cADRs, but factors other than cytokines are required for the onset of severe cADR. HMGB1 may contribute to the development of DIHS/DRESS through Th2 cell activation, which plays a key role together with Tregs in the disease. The involvement of HMGB1 in cADRs therefore requires further investigation.

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Conflicts of interest: none declared.

A case of pemphigus herpetiformis-like atypical pemphigus with IgG anti-desmocollin 3 antibodies

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Dear Editor, Pemphigus is an autoimmune blistering skin disease characterized by autoantibodies to keratinocyte cell surface antigens.[1] Major autoantigens for pemphigus are desmogleins (Dsgs), transmembrane cell–cell adhesion proteins belonging to the cadherin family. Dsg1 and Dsg3 are antigens for pemphigus foliaceus and pemphigus vulgaris, respectively. In addition to the four Dsg isoforms (Dsg1–4), there is another group of desmosomal cadherins, the desmocollins (Dsc), which is composed of three isoforms (Dsc1–3).

Pemphigus herpetiformis (PH) is a distinct variant of pemphigus; clinically it shows dermatitis herpetiformis-like features characterized by pruritic annular erythemas with vesicles on the periphery, histopathologically, eosinophilic spongiosis and immunologically, IgG antibodies to keratinocyte cell surfaces.[2] Ishii *et al.* reported that the targets of IgG autoantibodies in PH were Dsgs.[3] Anti-Dsg1 antibodies were detected in the majority of patients, while anti-Dsg3 antibodies were detected in some cases. In this study, we report a case of PH-like atypical pemphigus with IgG antibodies to Dsc3, but without antibodies to Dsgs.

A 57-year-old Japanese man visited us complaining of a 1-year history of erosive skin lesions. He was otherwise healthy with no particular medical history. Physical examination revealed pruritic, urticarial, annular erythemas on the trunk and extremities, with some showing small vesicles at the periphery (Fig. 1a). No mucosal involvement of the oral cavity was present. Blood tests and computed tomography showed no abnormalities.

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Letter to the Editor

TNF-α as a useful predictor of human herpesvirus-6 reactivation and indicator of the disease process in drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS)

Dear Editor,

Drug-induced hypersensitivity syndrome (DIHS), which is also referred to as drug reaction with eosinophilia and systemic symptoms (DRESS), is a multi-organ systemic reaction characterized by rashes, fever, leukocytosis with eosinophilia and atypical lymphocytes, liver dysfunction, and reactivation of human herpesvirus-6 (HHV-6) [1–4]. The mortality rate of DIHS/DRESS has recently been demonstrated to be 2–14% [3,4]. However, the pathogenesis of this serious syndrome has not been fully elucidated.

Whether reactivation of members of the Betaherpesvirinae subfamily, including HHV-6, occurs subsequent to drug hypersensitivity reactions is one of the major clinical focuses in diagnosis of DIHS/DRESS and selecting the most appropriate treatment for better outcomes in patients [1]. However, a useful, predictive marker of HHV-6 reactivation has not been widely accepted. Moreover, useful biomarkers that reflect the disease process of DIHS/DRESS have not been reported. Therefore, we conducted comparative assessments and detailed examinations of patients with DIHS/DRESS and measured their serum protein levels. We compared their serum levels with those of patients with other types of drug eruptions, such as erythema multiforme (EM) due to drugs/medications and Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN).

This study was approved by the Ethics Committee of Showa University School of Medicine. Diagnosis of DIHS/DRESS was determined according to the criteria established by the Japanese consensus group [1]. Diagnosis of SJS, overlap SJS/TEN, and TEN were performed according to criteria reported by Bastuji-Garin et al. [5]. Regarding selection of subjects for the study, 20, 4, and 7 patients who satisfied the full criteria for DIHS/DRESS, SJS/TEN (with an overlap of SJS/TEN patients; $n = 2$, and TEN patients; $n = 2$), and EM caused by drugs/medications [1,6] respectively, and for whom sufficient laboratory data were available. The dermatological manifestations of DIHS/DRESS are as follows: maculopapular rash-type, EM-type, and erythroderma [1,3]. Among the 20 DIHS/DRESS patients, there were 7 cases of maculopapular rash-type, 5 of EM-type, and 8 of erythroderma (Table 1).

In DIHS/DRESS cases, HHV-6 infection was evaluated by serum sample serological tests on admission and at various times thereafter. Titers of IgG and IgM to HHV-6 were determined using an indirect immunofluorescence antibody assay in all DIHS/DRESS patients, and serum HHV-6 DNA was measured in 18 of 20 patients using real-time polymerase chain reaction (PCR) [7]. We determined the serum levels of interleukin (IL)-6, tumor necrosis factor (TNF)-α, and IL-13 on admission and after recovery and compared them with those in patients with EM and SJS/TEN.

Anti-HHV-6 IgG titers were significantly increased in 13 of the 20 DIHS/DRESS patients. The presence of HHV-6 DNA in the serum of 18 patients was determined, and 10 patients tested positive for HHV-6 DNA (mean, 25.1 ± 7.5 days after onset in nine patients). In one patient in whom HHV-6 DNA was detected (Pt. 3, Table 1), anti-HHV-6 IgG titers were not increased significantly.

HHV-6 belongs to the Betaherpesvirinae subfamily, which contains two additional human herpesviruses: cytomegalovirus (CMV) and HHV-7 [1]. Previously, increased levels of proinflammatory cytokines such as TNF-α and IL-6 have been demonstrated with HHV-6 and CMV infection [8,9]. However, the exact mechanisms of reactivation of these viruses have not been fully elucidated. We determined the serum levels of TNF-α, IL-6, IL-13, C-reactive protein (CRP), and lactate dehydrogenase (LDH) in 14 patients with DIHS/DRESS whose serum had been stored for protein analysis on admission (Table 1), and compared these results between the HHV-6 reactivation and non-reactivation groups. The serum levels of TNF-α, CRP, and LDH before treatment were significantly higher in the HHV-6 reactivation group than in the HHV-6 non-reactivation group (TNF-α, $P = 0.0220$; CRP, $P = 0.0264$; LDH, $P = 0.0341$) (Fig. 1A–C). In our study, a TNF-α level of 12 pg/mL, a CRP level of 7 mg/dl, and a LDH level of 600 U/L were sufficient for detection of HHV-6 reactivation. Eight of fourteen patients satisfied the threshold of TNF-α. Levels of other proteins upon admission were not significantly correlated with either group. IL-13 was undetectable in the sera of all subjects.

Regarding conditions similar to DIHS/DRESS, Kamijima et al. recently reported the investigation of 28 patients with trichloroethylene hypersensitivity syndrome, including the reaction point of onset after exposure to trichloroethylene/drugs, clinical manifestations, blood examination, and period of virus reactivation [10]. They found that an elevated TNF-α level on admission was significantly correlated with an increase in HHV-6 DNA during the clinical course. This result supports our observation that an increasing level of TNF-α prior to the commencement of treatment may be an excellent biomarker for the early recognition of HHV-6 reactivation in patients with DIHS/DRESS.

Moreover, the TNF-α, CRP, and LDH levels decreased significantly in parallel with the response to treatment in only the DIHS/DRESS group (TNF-α, $P = 0.0418$; CRP, $P = 0.0001$; LDH, $P = 0.0026$) (Fig. 1D–F). To date, there have been no widely accepted biomarkers of the DIHS/DRESS disease process. Yoshikawa et al. reported elevated TNF-α levels in four of six DIHS/DRESS patients at onset [9]. These results indicate that the serum levels of these proteins reflect the DIHS/DRESS disease process; however, further investigation using a larger number of DIHS/DRESS samples is required.

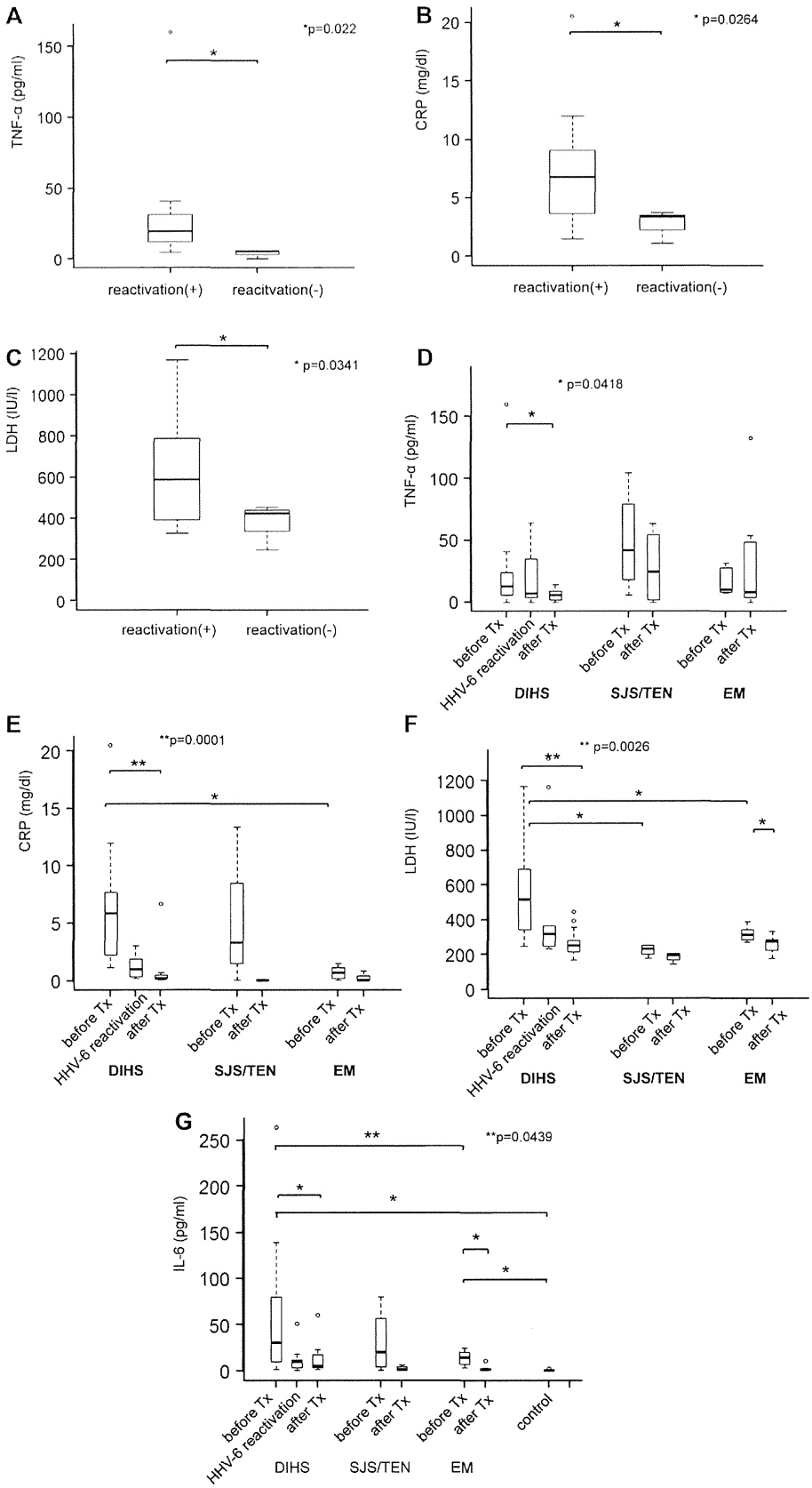

Fig. 1. Protein levels in the HHV-6 reactivation group and non-HHV-6 reactivation group in DIHS/DRESS ($n = 14$). In the DIHS/DRESS group, serum levels of TNF-α ($^*P < 0.05$) (Fig. 1A), CRP ($^*P < 0.05$) (Fig. 1B), and LDH ($^*P < 0.05$) (Fig. 1C) before treatment were significantly higher in the HHV-6 reactivation group than in the non-HHV-6 reactivation group. TNF-α, LDH, and CRP levels decreased significantly in parallel with the response to treatment in only the DIHS/DRESS group ($^*P < 0.05$) (Fig. 1D–F). The serum IL-6 levels on admission were significantly higher in the DIHS/DRESS group than in the EM group ($^*P < 0.05$) (Fig. 1G). The *t*-test and Mann–Whitney *U*-test were applied to evaluate differences in serum levels between the two groups. Regression analysis was also performed to elucidate trends in treatment responses. Correlations between two serum levels were examined using Pearson's correlation test. A *P*-value of <0.05 was considered to indicate statistical significance for all tests.

Table 1
Patient data (demographics, causative drugs, onset of symptoms, type of cutaneous eruption, systemic involvement, and HHV-6 reactivation).

Pt.	Age	Sex	Causative drug	Onset (days)	Type of eruption	Leukocytosis (/μl)	Eosinophilia (/mm^3)	Aty lym (%)	ALT (IU/L)	Cr (mg/dl)	HHV-6 reactivation	TNF-α (pg/ml)	CRP (mg/dl)	LDH (IU/l)
1	54	M	Phenytoin	41	Maculopapular	Yes (48,000)	Yes (3220)	Yes (3)	Yes (721)	Yes (6.63)	No	n.d.	n.d.	n.d.
2	35	F	Salazosulfapyridine	23	Maculopapular	Yes (13,700)	Yes (1781)	Yes (3)	Yes (1084)	Yes (1.13)	Yes	21.6	10.39	1005
3	65	M	Carbamazepine	58	EM-type	Yes (10,300)	No	No	Yes (81)	No	Yes	12.4	20.54	445
4	46	M	Carbamazepine	13	EM-type	Yes (10,600)	No (1038)	Yes (1)	Yes (87)	No	Yes	n.d.	n.d.	n.d.
5	32	M	Carbamazepine	21	Erythroderma	Yes (10,200)	No (1200)	Yes (14)	Yes (450)	No	No	n.d.	n.d.	n.d.
6	42	M	Carbamazepine	33	Maculopapular	Yes (16,900)	No (1183)	Yes (25)	Yes (131)	No	No	0	3.7	248
7	34	M	Phenobarbital	33	Maculopapular	Yes (10,700)	No	Yes (33.5)	Yes (890)	No	No	5.7502	3.4	425
8	27	M	Phenobarbital	14	Maculopapular	Yes (18,900)	Yes (2457)	Yes (17)	Yes (1156)	No	Yes	40.96	2.26	692
9	51	M	Allopurinol	12	Erythroderma	Yes (10,100)	No (441)	Yes (1)	Yes (118)	No	Yes	24.125	6.6	338
10	58	M	Carbamazepine	33	Erythroderma	Yes (16,800)	Yes (4872)	Yes (14)	Yes (242)	Yes (1.7)	Yes	13.075	6.8	883
11	49	M	Allopurinol	32	Erythroderma	Yes (17,100)	Yes (7182)	Yes (24)	Yes (302)	Yes (1.4)	Yes	38.819	7.7	588
12	86	M	Allopurinol	28	EM-type	Yes (17,500)	Yes (7500)	Yes (9)	Yes (65)	Yes (1.6)	Yes	19.678	5.1	584
13	54	F	Carbamazepine	27	Erythroderma	Yes (22,300)	Yes (1806)	Yes (24)	Yes (422)	Yes (1.5)	Yes	n.d.	n.d.	n.d.
14	74	M	Carbamazepine	35	Erythroderma	Yes (40,000)	Yes (4400)	Yes (3)	Yes (56)	No	Yes	10.133	6.9	344
15	69	M	Carbamazepine	30	EM-type	Yes (13,400)	Yes (1500)	Yes (1)	Yes (86)	No	Yes	4.494	12	326
16	47	M	Carbamazepine	78	Erythroderma	Yes (23,500)	Yes (8225)	Yes (6)	Yes (112)	No	Yes	n.d.	n.d.	n.d.
17	35	M	Carbamazepine	12	EM-type	Yes (15,000)	Yes (1500)	Yes (7)	Yes (213)	No	No	5.8931	1.1	453
18	30	M	Trichloroethylene	21	Erythroderma	Yes (21,700)	Yes (5425)	Yes (13)	Yes (391)	Yes (2.0)	Yes	159.864	1.8	659
29	45	F	Carbamazepine	31	Maculopapular	Yes (12,100)	No (630)	No	Yes (139)	No	No	n.d.	n.d.	n.d.
20	55	F	Mexiletine	50	Maculopapular	Yes (15,100)	Yes (9966)	Yes (23)	Yes (75)	No	Yes	11.748	1.5	1168

All patients with a diagnosis of DIHS/DRESS were treated at Showa University Hospital, Department of Dermatology, between August 2001 and March 2013. The study population comprised 16 males and 4 females ranging in age at the time of the initial examination from 27 to 86 years, with a mean age of 49.3 ± 15.7 years in the DIHS/DRESS group. The mean duration from the initial exposure to the suspected medication until the onset of DIHS/DRESS was 31.2 ± 16.3 days. White blood cell counts exceeding 11,000/μL (normal range 3500–9000/μL) at the initial examination were found in 15 patients (75%). During the clinical course, eosinophilia (≥1500/mm^3; normal range 70–440/μL) was noted in 13 patients (65%). Atypical lymphocytes were found in 18 of 20 patients (90%), and 12 of 20 patients (60%) had >5% atypical lymphocytes. All patients had hepatic abnormalities (alanine aminotransferase (ALT) above the normal range of 5–25 IU/L), and 14 patients (70%) had a serum ALT >100 IU/L. Seven patients (35%) had renal dysfunction, one of whom was on continuous dialysis. HHV-6 DNA of Pt. 16 was positive during the entire course of their illness because of chromosomal integration of HHV-6 DNA.
CRP; C-reactive protein (normal range <0.2 mg/dl), LDH; lactate dehydrogenase (normal range 105–220 U/L).
Onset (day), onset of symptoms (day); Aty Lym (%), Atypical lymphocytosis (%); ALT (IU/L), hepatitis (maximum of ALT (IU/L)); Cr (mg/dl), renal impairment (Cr (mg/dl)); eosinophilia (/mm^3), eosinophilia (≥1500/mm^3); n.d., not done.

Finally, the serum IL-6 levels on admission were significantly higher in the DIHS/DRESS group than in the EM group ($P = 0.0439$) (Fig. 1G). Some DIHS/DRESS patients manifest targetoid erythematous lesions; such patients may be clinically similar to those with EM due to drugs/medications, especially in the early stage of the disease course. In fact, 5 of 20 patients showed targetoid erythematous skin manifestations. Based on our investigation, IL-6 could be a good marker for the early recognition of DIHS compared with EM.

In conclusion, we herein present a large case series involving a single-facility survey of DIHS/DRESS in Japan. This study suggests that elevated TNF-α during the early onset stage is a good marker for the early recognition of HHV-6 reactivation. The TNF-α level also reflects therapeutic responses and could be a useful marker of the DIHS/DRESS disease process. Early and careful recognition of these factors make it possible to choose an appropriate treatment and improve patient outcomes.

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Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms with histologic features mimicking cutaneous pseudolymphoma

Dear Editor,

Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS) may be included in the broad classification of drug-induced pseudolymphoma. However, these conditions seem to be two distinct entities, with different clinical features and outcomes.[1] We report a case of DIHS/DRESS showing histologic features of cutaneous pseudolymphoma.

A 31-year-old man presented with a 10-day history of high fever and generalized rash. He suffered from bipolar depression and had been treated with sodium valproate. Twenty-one days after adding carbamazepine, high fever developed, followed by

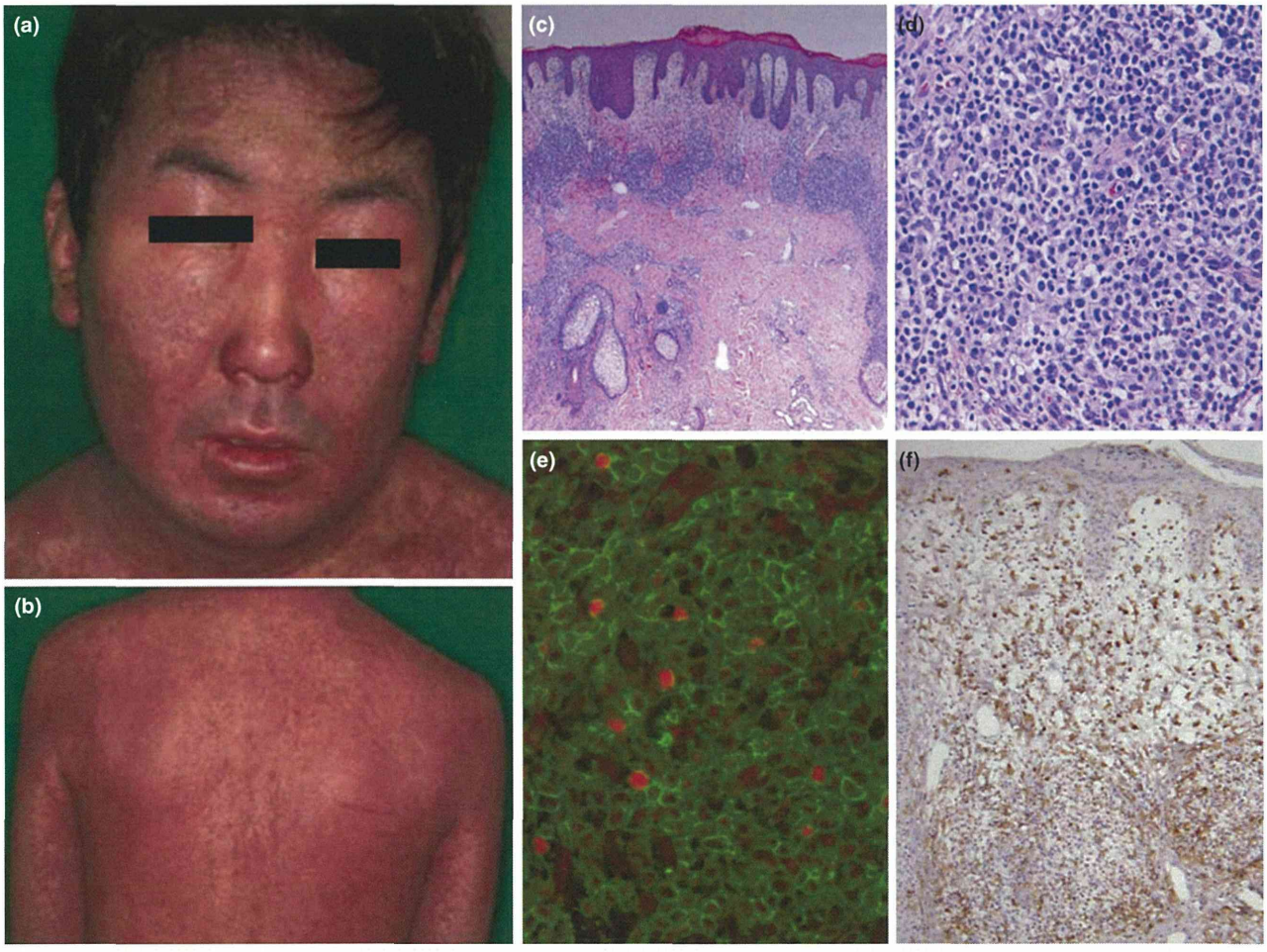

Figure 1. (a, b) Patient clinical features. Erythroderma with edematous swelling of the face. (c, d) Histology of the neck skin. Well-demarcated patches of infiltrates around the dermal vessels and folliculosebaceous units (c: hematoxylin-eosin, 40×). Dense infiltrates consisted of lymphoid cells predominantly with occasional atypical nuclei and minimal nuclear debris (d: hematoxylin-eosin, 400×). (e) Double immunofluorescence labeling of CD3 (green) and FoxP3 (red) revealed 10 double-positive cells in infiltrates per high-power field (1000×). (f) Large numbers of $CD16^+$ monocytes were observed in edematous dermal papillae and the peripheries of the dense infiltrates (100×).

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extensive erythematous plaques, lymphadenopathy and liver dysfunction. Examination revealed erythroderma on the whole body (Fig. 1a,b). Cervical, axillary, and inguinal lymph nodes were swollen. Sodium valproate and carbamazepine were discontinued, and the patient was admitted for suspected DIHS/DRESS. Laboratory findings on admission were as follows: white blood cell count 29 400/μL (eosinophils 7%, atypical lymphocytes 34%); AST 119 IU/mL; ALT 318 IU/mL; LDH 1105 IU/mL; γ-GTP 806 IU/mL; and soluble IL-2 receptor 2130 U/mL. Histology of the neck skin revealed edematous dermal papillae and well-demarcated patches of infiltrates around the dermal vessels and folliculosebaceous units. Dense infiltrates consisted predominantly of lymphoid cells with occasional atypical nuclei (Fig. 1c,d). By immunohistochemistry, most infiltrates were $CD3^+$ T-cells with higher expression of $CD8^+$ than $CD4^+$. Double immunofluorescence labeling of infiltrates revealed 7–10 $CD3^+FoxP3^+$ cells per high-power field (Fig. 1e). Cells labeled for B cell markers such as CD20 and CD79a were few. Large numbers of $CD16^+$ monocytes were distributed in edematous dermal papillae and the peripheries of the dense infiltrates (Fig. 1f), whereas $CD14^+$ cells were few, as reported in a DIHS/DRESS case series.[2] Prednisone (0.7 mg/kg/day, drip infusion) was started and slowly tapered. Serum HHV-6 DNA was detected 20 days after the onset of disease. Anti-HHV-6 IgG titers increased significantly (from 40× to 2560×) in paired sera. A drug-induced lymphocyte stimulation test performed at day 112 of the disease course was positive for carbamazepine (SI index 19.51) and sodium valproate (SI index 3.53).

Callot *et al.*[1] endeavored to separate the two conditions retrospectively, based on 24 cases and an additional 95 published cases. The pseudolymphoma group demonstrated subacute papulonodular or infiltrated plaques devoid of visceral involvement.[1] Histology revealed dense lymphocytic infiltrates and occasional Pautrier's microabscess mimicking lymphoma.[3,4] In contrast, the DIHS/DRESS group had acute widespread rash with high fever, lymphadenopathy, and multivisceral involvement.[1] Systemic involvement, such as extensive lymphadenopathy and peripheral blood leukocytosis with atypical lymphocytosis were suggestive of pseudolymphoma, whereas histology of the skin was usually not specific. In the present case, the clinical manifestation was DIHS/DRESS, while the histology mimicked pseudolymphoma. This case suggested some features of pseudolymphoma in DIHS/DRESS, although the two entities are distinct. Dramatic expansion of functional regulatory T-cells (Tregs) in peripheral blood and abundant Tregs in the dermis of DIHS/DRESS patients have been reported.[5] A number of $CD3^+FoxP^+$ cells, presumably Tregs, were found in the dense infiltrates in our case. Although the ratio to $CD3^+$ cells was not higher than for usual DIHS/DRESS, Tregs might serve to prevent the further activation and expansion of effector T cells.

CONFLICT OF INTEREST: None.

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Immediate-onset anaphylaxis of *Bacillus subtilis*-fermented soybeans (*natto*)

Dear Editor,

I read the Letter to the Editor entitled "Involvement of poly (γ-glutamic acid) as an allergen in late-onset anaphylaxis due to fermented soybeans (*natto*)" by Inomata *et al.*[1] with interest. *Natto* is a traditional Japanese preserved food made by fermenting soy beans with *Bacillus subtilis natto*, a type of hay bacillus. In recent years, there have been increasing opportunities to consume *natto* throughout the world, due to the boom in health foods and Japanese foods. Unlike ordinary food allergies, *natto* anaphylaxis is distinguished by symptoms that appear with a delay of 5–12 h after ingesting *natto*.[1–4] To our knowledge, we report the first case of immediate-onset ana-

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セツキシマブによるアナフィラキシーショックの４例—α-gal 特異的 IgE 検出による回避の可能性—

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要 旨

セツキシマブによるアナフィラキシーショックの４例を経験した．糖鎖 α-gal が原因の牛肉アレルギーでは交差反応のためにセツキシマブアレルギーを生じるため，血清中牛肉特異的 IgE を定量したところ４例中３例で検出された．ウェスタンブロット法にて全例でセツキシマブ特異的 IgE が検出され，CAP-FEIA 法にて全例で α-gal 特異的 IgE が検出された．事前に牛肉，セツキシマブ，α-gal 特異的 IgE などを検索することにより，α-gal が原因のアナフィラキシーショックを回避することが可能であると考える．

はじめに

我々はこれまでに，本邦における牛肉アレルギー患者の主要原因抗原が米国における報告と同様に糖鎖 galactose-α-1, 3-galactose（α-gal）であること，これらの患者は豚などの哺乳類肉，カレイ魚卵，抗悪性腫瘍剤のセツキシマブと交差反応することを報告した[1) 2)]．特にセツキシマブは直接静脈内投与するために，これらの患者では重篤なアレルギー症状を誘発する可能性があり，啓発の必要性を訴えていた[2)]．今回 α-gal が原因と思われるセツキシマブによるアナフィラキシーショックの４例を実際に経験したので報告する．

症例提示

症 例１：66 歳女性．

既往歴：特記することなし．

現病歴：2013 年３月某日，喉頭癌と左鎖骨上窩リンパ節転移に対して，放射線治療後にセツキシマブの投与が開始された．初回投与開始 10 分後に，全身のそう痒感と呼吸苦が出現した．さらに，全身の冷汗と上肢の発赤が出現し，血圧が低下（収縮期血圧 60 mmHg，拡張期血圧測定不能）した．インフュージョンリアクションを疑われ，直ちにセツキシマブ投与中止の上で輸液と酸素投与が開始され，症状は徐々に改善した．

症 例２：81 歳男性．

既往歴：65 歳頃にカレイ魚卵摂取後に蕁麻疹が出現した．

現病歴：2013 年６月某日，中咽頭癌に対してセツキシマブの投与が開始された．初回投与開始 15 分後に，顔面の発赤が出現した．17 分後には顔面の発赤腫脹の増悪と呼吸苦が出現し，その後血圧が低下（収縮期血圧 50 mmHg，拡張期血圧測定不能）し意識消失した．インフュージョンリアクションを疑われ，直ちにセツキシマブの投与中止の上でアドレナリン静注と輸液と酸素投与が開始され，症状は徐々に改善した．

症 例３：60 歳男性．

既往歴：特記することなし．

現病歴：2013 年６月某日，喉頭癌と口腔底癌に対して，放射線治療と並行してセツキシマブの投与が開始された．初回投与開始 10 分後に，全身のそう痒と顔面の発赤が出現し，15 分後には冷汗が著明となり血圧が低下（55/38 mmHg）した．インフュージョンリアクションを疑われ，直ちにセツキシマブの投与中止の上でアドレナリン筋注と輸液と酸素投与が開始され，症状は徐々に改善した．

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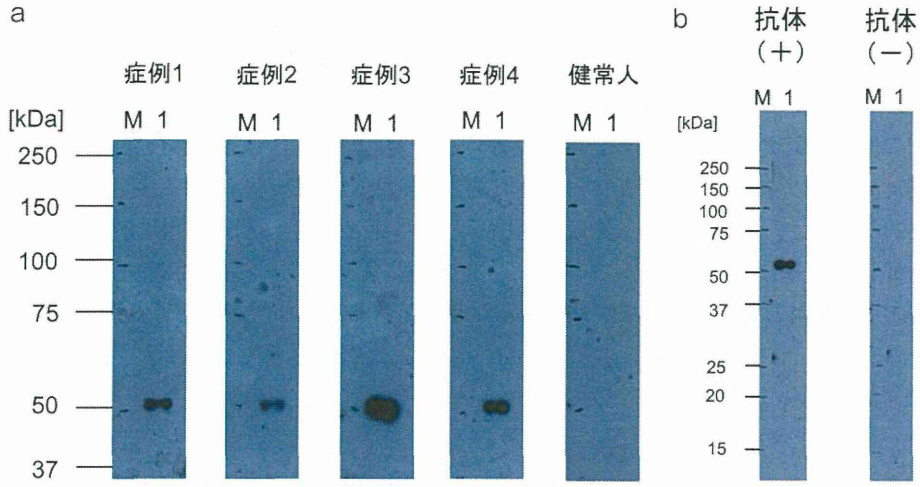
図 1

a 患者血清 IgE を用いたウェスタンブロット解析
全例でセツキシマブ H 鎖の泳動領域中の 50 kDa 付近の蛋白質に相当するバンドがみられた．M：分子量マーカー，レーン 1：セツキシマブ．

b セツキシマブ中の α-gal の検索
抗 α-gal 抗体を用いてセツキシマブ中の α-gal の検索を行ったところ，セツキシマブ由来の 50 kDa 付近の蛋白質に α-gal が存在することが確認された．M：分子量マーカー，レーン 1：セツキシマブ．



症例 4：67 歳男性．

既往歴：特記することなし．

現病歴：2013 年 7 月某日，上咽頭癌と両側頸部リンパ節転移，肺転移に対して，放射線治療や各種化学療法施行後にセツキシマブの投与が開始された．初回投与開始 13 分後に，咳漱と咽頭違和感が出現し，意識朦朧となり血圧が低下（49/18 mmHg）した．尿失禁，嘔吐などが出現し，インフュージョンリアクションを疑われ，直ちにセツキシマブの投与中止の上でアドレナリン静注と輸液と酸素投与が開始され，症状は徐々に改善した．経過中，皮疹の出現は確認されていない．

血清中抗原特異的 IgE 検査結果

ウェスタンブロット法

セツキシマブ（メルクセローノ株式会社，東京）をサンプルバッファーで 20 ng/mL に希釈してポリアクリルアミド電気泳動（25 μg/Lane）に供し，PVDF 膜に転写後，患者血清を反応させた．血清中抗原特異的 IgE の検出には，ペルオキシダーゼ標識抗ヒト IgE 抗体（KPL 社，Gaithersburg，USA）と ECL Prime（GE ヘルスケア・ジャパン株式会社，東京）を用いた．全例で，セツキシマブ H 鎖の泳動領域中の 50 kDa 付近の蛋白質に相当するバンドがみられた（図 1a）．ウェスタンブロット法における患者血清中 IgE のセツキシマブへの結合が特異的なものであるか否かを確認する目的で，セツキシマブ（10 ng，100 ng，1 μg）を患者血清 50 μl と予め 37℃ で 2 時間反応させて特異的 IgE をセツキシマブと結合させ，ウェスタンブロット法に供したところ，患者血清中 IgE のセツキシマブへの結合は，患者血清と予め反応させたセツキシマブの濃度に依存して減弱，消失した．このことより，本結合がセツキシマブ特異的なものであることが確認された

さらに，セツキシマブ中の α-gal の有無を検索するために，セツキシマブ 20 ng を泳動後，抗 α-gal マウス IgM 抗体（エンゾ・ライフサイエンス社，NY，USA）をブロッキングバッファーで 5 μl/mL に希釈したものを一次抗体として用いてウェスタンブロット法を施行した．α-gal の検出にはペルオキシダーゼ標識抗マウス IgM 抗体（KPL 社，Gaithersburg，USA）と ECL Prime（GE ヘルスケア・ジャパン株式会社，東京）を用いた．その結果，セツキシマブ由来の 50 kDa 付近の蛋白質に α-gal が存在することが確認された（図 1b）．

CAP-FEIA 法

サーモフィッシャーサイエンティフィック社の供給する CAP-FEIA 法により，牛肉特異的 IgE および牛