SHORT COMMUNICATION

Predominant Contribution of CD4 T Cells to Human Herpesvirus 6 (HHV-6) Load in the Peripheral Blood of Patients with Drug-induced Hypersensitivity Syndrome and Persistent HHV-6 Infection

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Drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe adverse cutaneous drug reaction associated with the reactivation of human herpesvirus 6 (HHV-6). In DIHS, HHV-6 is generally reactivated 2–3 weeks after the onset of a rash, and such reactivation is associated with the flare-up of clinical symptoms (1). The reactivation of HHV-6 usually occurs as a transient event; however, in rare cases HHV-6 DNA continues to be detected long after the onset of the condition, which is sometimes associated with frequent recurrence of clinical symptoms, such as skin rashes. There has been only one report of a case of DIHS involving a persistent HHV-6 infection (2). We report here 3 cases of DIHS in which HHV-6 DNA was detected in the patients' peripheral blood mononuclear cells (PBMC) long after resolution of their DIHS. We also demonstrated that CD4 T cells were the main contributors to the PBMC HHV-6 DNA load throughout the patients' clinical courses, while in the early stages of their conditions CD14$^+$ monocytes and other types of PBMC also harboured HHV-6 DNA.

PATIENTS AND METHODS

The characteristics of the 3 patients with DIHS are listed in Table SI[1]. Blood samples were obtained from each patient after the onset of a rash. PBMC were isolated from whole blood by Ficoll gradient separation (GE Healthcare, Little Chalfont, UK) and divided into 2–3 aliquots. Sera were separated from whole blood by centrifugation. An aliquot of PBMC and an aliquot of serum were subjected to real-time polymerase chain reaction (PCR) to detect and quantify HHV-6 DNA. Briefly, DNA was isolated from PBMC or serum using the QIAamp DNA blood mini kit (QIAGEN, Hilden, Germany), according to the manufacturer's protocol. Real-time PCR was performed with the TaqMan fast advanced master mix (Applied Biosystems, Foster City, CA, USA) and the following primers and probe (3): forward primer: GAAGCAGCAATCGCAACACA, probe: AACCCGTGCGCCG-CTCCC, reverse primer: ACAACATGTAACTCGGTGTACGGT. The PCR and data collection were conducted on an Applied Biosystems StepOnePlus real-time PCR system. A further aliquot of PBMC was subjected to magnetic bead purification (Miltenyi Biotec, Bergisch Gladbach, Germany) to obtain CD14$^+$ cells. The rest of the cell fraction was subsequently used to purify the CD4 T-cell fraction. The HHV-6 DNA load of each cell type was then measured by real-time PCR. In some experiments, a further aliquot of PBMC was subjected to CD16$^+$ cell isolation followed by CD8 T-cell isolation using magnetic beads. To detect the U31, U39, U90, and U94 gene transcripts, purified CD4 T cells from PBMC were cultured with 5 μg/ml phytohaemagglutinin (PHA) and 20 units/ml recombinant human interleukin 2 in GIT medium (WAKO, Tokyo, Japan). Seven days later, the cells were harvested and subjected to RNA extraction using an RNeasy plus kit (QIAGEN) followed by cDNA synthesis using a high-capacity RNA-to-cDNA kit (Applied Biosystems). Real-time PCR was carried out using specific primers and probes.

RESULTS AND DISCUSSION

As shown in **Fig. 1**A, HHV-6 DNA was detected at relatively high copy numbers long after resolution of the patients' DIHS, although the amounts of DNA detected at these time-points were lower than those seen during the early phase of the condition, except in case 3, in which HHV-6 DNA was detected on the day of admission (day 8).

Since little is known about which types of PBMC harbour HHV-6 in DIHS patients with persistent HHV-6 infections, we next evaluated the HHV-6 DNA loads of CD4 T cells, CD14$^+$ cells, and the remaining PBMC obtained from the 3 patients. During the early phase of the patients' DIHS, HHV-6 DNA was detected in all cell types, with CD4 T cells being the predominant cell type. At later time-points, CD4 T cells seemed to harbour the majority of the HHV-6 DNA load (Fig. 1B).

HHV-6 was found to mainly infect and replicate in CD4 T cells. However, HHV-6 is able to infect a wide variety of cell types, including natural killer cells and dendritic cells (4). In the latent state, HHV-6 is reported to persist in monocytes/macrophages (4). In some cases, HHV-6 DNA could not be detected in PBMC from healthy individuals with latent HHV-6 infections (4), whereas in others low levels of HHV-6 DNA (around 2 log10 copies/ml) were detected (5, 6).

In our study, no HHV-6 DNA was detected in the patients' sera at later time-points (Fig. 1A), and while the patients' anti-HHV-6 IgG titres increased during the early stages of their conditions they subsequently started to decline (Table SI[1]), which is not consistent with reactivation. These findings suggest that latent HHV-6 persisted in the patients' CD4 T cells at later time-points. However, the amounts of HHV-6 DNA and the types of cells harbouring HHV-6 DNA (CD4 T cells) at later time-points cannot be fully explained by a latent infection. To distinguish between HHV-6 reactivation and latency at later time-points, we examined the expression of 4 HHV-

[1]https://www.medicaljournals.se/acta/content/abstract/10.2340/00015555-2791

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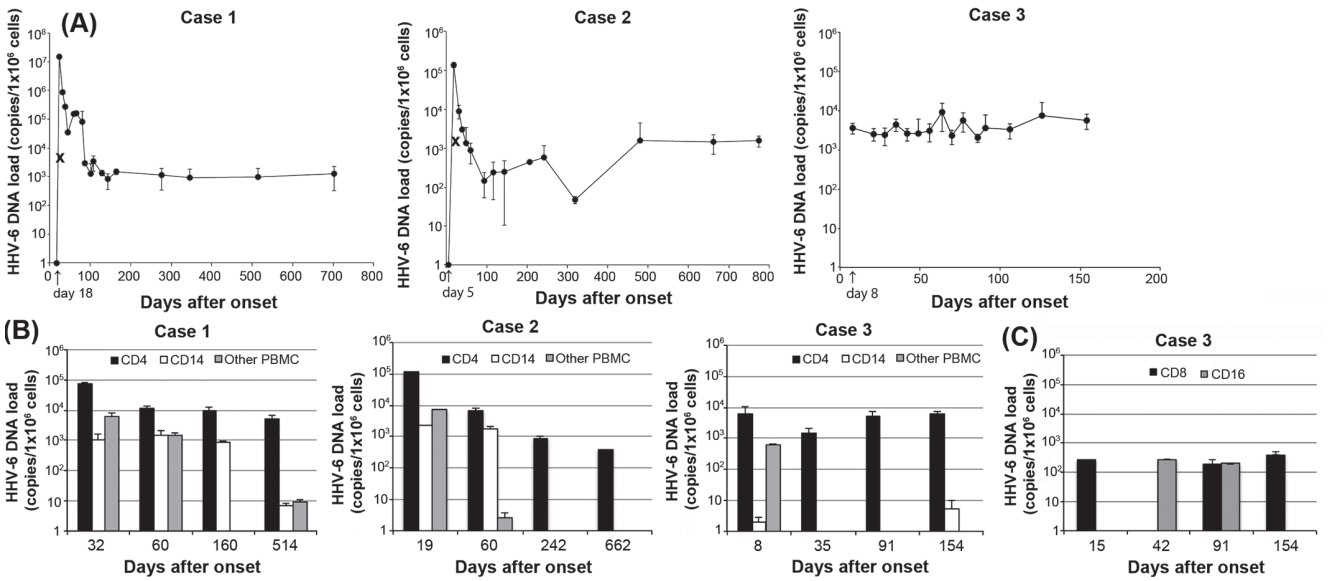

Fig. 1. Human herpesvirus 6 (HHV-6) DNA load (log scale) in peripheral blood mononuclear cells (PBMC). (A) Real-time PCR was performed with PBMC obtained from 3 drug-induced hypersensitivity syndrome (DIHS) patients. Triplicate experiments, results presented as mean and standard deviation. The *arrow* indicates the day of admission (when the first sample was collected). × indicates the serum HHV-6 DNA load (copies/ml). HHV-6 DNA was only detected in the patients' sera when the HHV-6 DNA load of the PBMC was at its peak. (B) Real-time PCR was performed with purified CD4 T cells, $CD14^+$ cells, and the other cells left after the isolation of CD4 T cells and $CD14^+$ cells from the PBMC. The CD4 T cells exhibited a higher HHV-6 DNA load than the $CD14^+$ cells and the remaining PBMC in the early phase. Later, HHV-6 DNA was mainly detected in CD4 T cells. (C) Real-time PCR was performed with purified CD8 T cells and $CD16^+$ cells obtained from case 3.

6 gene transcripts, U31, U39, U90, and U94, in CD4 T cells that had been stimulated with PHA. U31 and U39 encode HHV-6 late proteins. U90 is an immediate early gene transcript, and U94 is a putative latency-associated gene transcript (7). Real-time PCR showed that the U90 gene transcript, but not the other 3 gene transcripts, was detected at a low level in CD4 T cells from case 3 on day 77 after onset (data not shown). These results suggest that low-level HHV-6 reactivation that did not have an influence on the viral antibody titre persisted in case 3.

It has been reported that the number of circulating monomyeloid precursors with the $CD11b^+CD13^+CD14^-CD16^{high}$ phenotype increases in the early stages of DIHS and that these cells harbour the HHV-6 antigen (8). Thus, we examined the expression of HHV-6 DNA in $CD16^+$ cells in case 3 (Fig. 1C). Although we were able to detect small amounts of DNA in the $CD16^+$ cells as well as in the CD8 T cells, CD4 T cells served as the main HHV-6 reservoir throughout the course of the patient's DIHS (Fig. 1B).

Why is HHV-6 DNA persistently detected in some cases of DIHS? HHV-6 infections are frequently encountered in immunosuppressed patients, such as bone marrow transplant recipients (9) and patients with AIDS (5). In DIHS, reductions in immunoglobulin levels and B-cell counts (10), and the marked expansion of functional regulatory T cells (11) have been considered to cause immunosuppression. However, these immunosuppressive conditions occur only in the acute stage of DIHS, which could facilitate HHV-6 reactivation (10, 11). It remains unclear whether our patients were in an immunosuppressed state even after their recovery.

Occasionally, healthy individuals have been shown to have persistently high HHV-6 DNA levels originating from chromosomally integrated HHV-6 (6). The whole-blood HHV-6 DNA levels of immunocompetent individuals that have undergone chromosomal HHV-6 integration are characteristically high (around 6 log10 copies/ml) (6). We investigated cases 2 and 3 for HHV-6 chromosomal integration by examining the patients' hair follicles. HHV-6 DNA was not detected in their hair follicles (data not shown), indicating that HHV-6 chromosomal integration had not occurred in these cases. Although the possibility of HHV-6 chromosomal integration was not investigated in case 1, the fact that no HHV-6 DNA was detected at the initial visit (day 18) and relatively low levels of HHV-6 DNA were detected at later time-points suggest that case 1 did not involve chromosomally integrated HHV-6.

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Table SI. Clinical details of patients with drug-induced hypersensitivity syndrome and persistent human herpesvirus 6 (HHV-6) infection

Characteristics	Case 1		Case 2		Case 3	
Age, years/Sex	84/F		81/M		39/M	
Suspected drug	Allopurinol		Allopurinol		Carbamazepine	
Interval between drug intake and rash onset, days	42		41		81	
Fever	≥ 38°C		Unknown		≥ 38°C	
White blood cells, /ml	6,300		29,000		17,300	
Eosinophils, ml	800		600		900	
Atypical lymphocytes, %	6		3		0	
ALT, IU/l	50		37		78	
Creatinine (mg/dl)	1.16		5.79		0.66	
Anti-HHV-6 IgG titre	Day 32	320	Day 5	20	Day 7	40
	80	80	19	20	21	80
	143	40	60	80	63	160
	514	40	242	40	154	80
			662	40		

Normal ranges: white blood cells: 3,300–8,600/ml; alanine aminotransferase (ALT): 10–42 U/l (males) and 7–32 U/l (females); creatinine, 0.65–1.07 mg/dl (males) and 0.46–0.79 mg/dl (females); anti-HHV-6 IgG, ×10–×40.

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薬剤性過敏症症候群とTARC

Drug-induced hypersensitivity syndrome（DIHS） and thymus and activation-regulated chemokine（TARC）

浅田 秀夫

summary

薬剤性過敏症症候群（drug-induced hypersensitivity syndrome：DIHS）は，限られた薬剤により遅発性に発症し，発熱，多臓器障害，ヒトヘルペスウイルス再活性化を伴う重症型薬疹の1つである．本症では，初期の対応がその後の経過を左右するため，早期診断が必要不可欠である．しかし実際には，問診や臨床所見のみから，DIHSを早期に診断するのは困難なことが多い．近年，DIHSの発症初期に，Th2型免疫反応を誘導するケモカインの1つであるthymus and activation-regulated chemokine（TARC）の血清中濃度が著明に高値を示すことが明らかとなった．一方，Stevens-Johnson症候群，中毒性表皮壊死症，紅斑丘疹型薬疹では，軽度の上昇にとどまることから，TARCがDIHSの早期診断のバイオマーカーとして注目されている．

key words 薬剤性過敏症候群，thymus and activation-regulated chemokine（TARC），ケモカイン，バイオマーカー，HHV-6

浅田秀夫：臨皮 71（5増）：66-69，2017

はじめに

薬剤性過敏症症候群（drug-induced hypersensitivity syndrome：DIHS）とは，抗けいれん薬などの比較的限られた薬剤により引き起こされ，発熱や多臓器障害を伴う重症型薬疹の1つである．薬剤投与開始から3週間以上経って遅発性に発症し，皮疹は紅斑丘疹型（時に多形紅斑型）に始まって紅皮症となることが多い．皮疹だけでなく，リンパ節腫脹，発熱，異型リンパ球の出現や好酸球増多，肝障害，腎障害などの症状を認め，原因薬剤中止後も，しばしば皮疹や臓器障害が遷延する．発症後2～4週後にHHV-6の再活性化を生じることが判明し，薬剤アレルギーとウイルス感染症の複合した新たな病態として認識されている[1,2]．DIHSでは病初期の対応がその後の経過を左右するため，早期診断が必要不可欠である．しかし，投薬歴，特有の顔貌，発熱などから本疾患が疑われても，初期には播種状紅斑丘疹型薬疹（maculopapular exanthema：MPE）やStevens-

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〔略語〕DIHS：drug-induced hypersensitivity syndrome，MPE：maculopapular exanthema，SJS：Stevens-Johnson syndrome，TARC：thymus and activation-regulated chemokine，TEN：toxic epidermal necrolysis，Treg：regulatory T cell

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Johnson 症候群（Stevens-Johnson syndrome：SJS）との鑑別に悩まされることが多い．近年，Th2 型免疫反応を誘導するケモカインの 1 つである thymus and activation-regulated chemokine（TARC）の血清中の濃度が DIHS の発症初期から著明に高値を示すのに対して，SJS/中毒性表皮壊死症（toxic epidermal necrolysis：TEN）や MPE では，軽度の上昇にとどまることが明らかとなった[3~5]．本稿では，TARC に焦点を当てて，DIHS の早期診断のバイオマーカーとしての有用性，HHV-6 再活性化と TARC との関わりについて解説する．

DIHS における血清 TARC 値の推移

TARC/CCL17 は CC ケモカインの 1 つで，CC ケモカイン受容体の一種である CCR4 に結合する．CCR4 は Th2 細胞，制御性 T 細胞（regulatory T cell：Treg 細胞）などの表面に発現しており，これらの T 細胞サブセットが担う免疫反応において重要な役割を果たしている．現在，TARC はアトピー性皮膚炎の疾患活動性マーカーとして広く用いられているが，アトピー性皮膚炎以外にも炎症性皮膚疾患に伴う紅皮症などで，血清 TARC 値が上昇することが報告されている[6]．

DIHS では，しばしば紅皮症に進展し，Th2 型免疫反応の好酸球増多や，急性期の Treg の増加[7]といった現象がみられるが，これらの現象は TARC の作用とよく合致している．このような背景から，われわれは DIHS の病態形成に TARC が重要な役割を担っているのではないかと考え，臨床症状と血清 TARC 値との関係を経時的に調べた．その結果，血清 TARC 値は DIHS 急性期に著明に上昇することが明らかとなり，その推移は皮疹の活動性とよく相関していた（**図 1**）[3]．TARC のピークは通常，HHV-6 再活性化に先行してみられ，皮疹の消退とともに速やかに低下し，HHV-6 再活性化時にはすでに低下していることが多い．

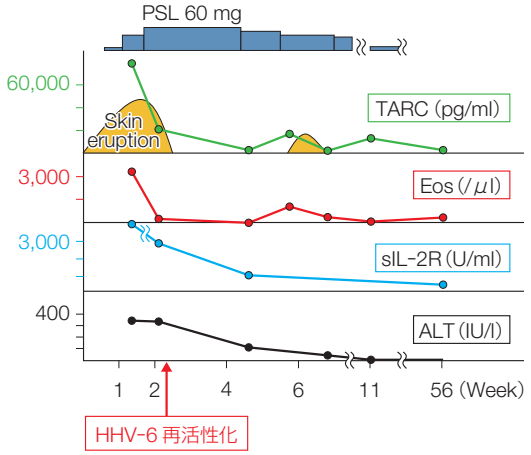

図 1　薬剤性過敏症症候群における血清 TARC 値の推移
（文献 3 より引用改変）

DIHS で上昇する TARC はどの細胞に由来するのか？

DIHS 皮疹部の生検組織について，抗ヒト TARC 抗体を用いた免疫組織化学染色を行った結果，真皮に浸潤する樹状細胞様の形態をした細胞の一部に TARC の発現がみられた（**図 2**）[3]．そこで，真皮樹状細胞の表面マーカーの 1 つである CD11c と TARC の二重染色を行った結果，CD11c 陽性樹状細胞の一部で TARC の発現が確認された．以上より，皮疹部に浸潤する CD11c 陽性真皮樹状細胞が DIHS における TARC の産生源の 1 つであろうと考えられる[3]．

DIHS のバイオマーカーとしての TARC の有用性

DIHS では時に致命的な経過をたどることがあるが，病初期の対応がその後の経過や予後を左右する．また DIHS の治療は，他の薬疹とはかなり異なっている．すなわち DIHS では，一般にステロイドの全身投与を必要とするが，HHV-6 やサイトメガロウイルスなどの再活性化を伴うことから，SJS/TEN の場合とは異なりステロイドパルス療法のようなステロイド量の急激な変動は好ましくなく，中等量（0.5～1 mg/kg）から開始し再

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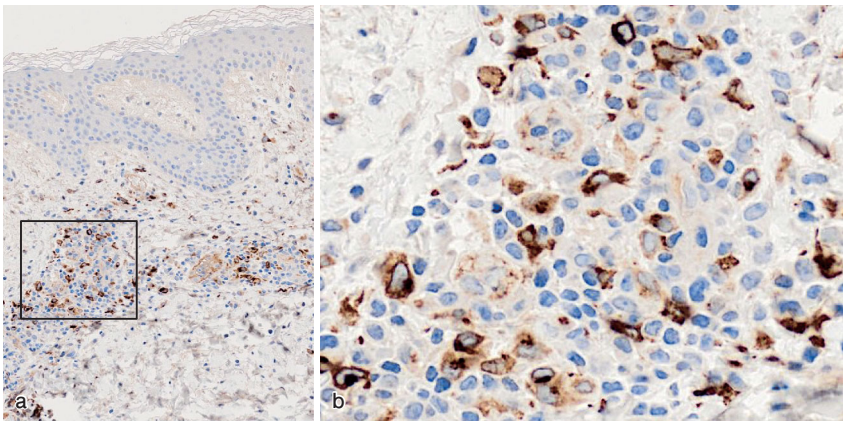

図 2　薬剤性過敏症症候群(DIHS)皮疹部における TARC の発現
DIHS 皮疹部からのパラフィン切片を用いて，抗ヒト TARC 抗体による免疫染色を行った．真皮に浸潤する樹状細胞様細胞に発現がみられた(b は a 枠内の拡大像)．
(文献 3 より引用改変)

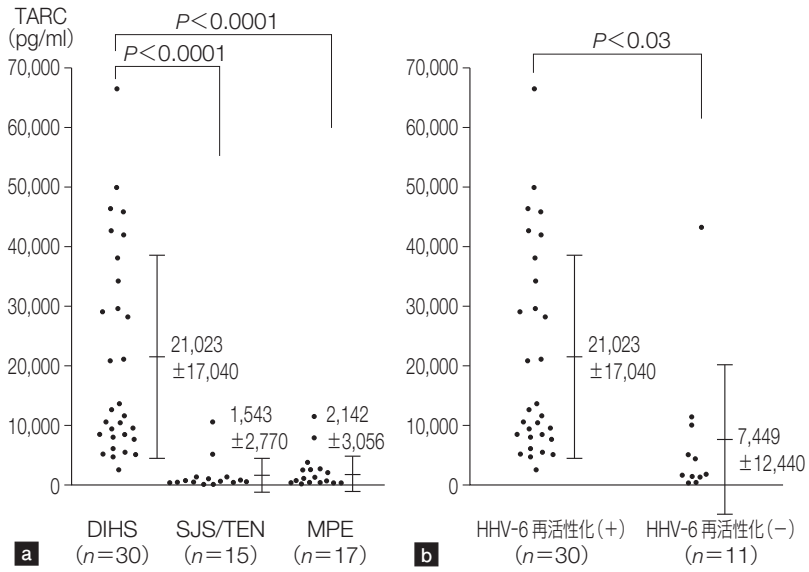

図 3　薬疹の型ならびに HHV-6 再活性化と血清 TARC 値との関係
a：DIHS，SJS/TEN，MPE の急性期における血清 TARC 値の比較．
b：HHV-6 の再活性化を伴った典型 DIHS と再活性化を伴わなかった DIHS 類似薬疹の急性期における TARC の比較．
DIHS : drug-induced hypersensitivity syndrome(薬剤性過敏症症候群)，SJS/TEN : Stevens-Johnson syndrome(Stevens-Johnson 症候群)/toxic epidermal necrolysis(中毒性表皮壊死症)，MPE : maculopapular exanthema(播種状紅斑丘疹型薬疹)
(文献 4 より引用改変)

燃に注意しつつ慎重に漸減する方法が推奨されている[8~10]．したがって，適切な治療を行うためには早期診断が必要不可欠である．しかし，投薬歴や特有の顔貌，発熱などから本疾患が疑われても，発症早期には MPE や SJS との鑑別にしばしば悩まされる．すなわち DIHS の診断基準に含まれる「原因薬剤中止後の 2 週間以上の経過の遷延」，「HHV-6 の再活性化」などの項目は，病初

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期においては判定不可能であるため，診断に苦慮することになる．そのため客観的かつ迅速な診断法の開発が望まれている．

そこでわれわれは，DHIS早期診断のバイオマーカーとしての血清TARCの有用性について検証を試みた．DIHS 30例，SJS/TEN 15例，MPE 17例について，急性期血清中のTARC値を比較したところ，DIHS患者群では平均21,023 pg/mlと，著明な上昇を認めたのに対して，SJS/TENおよびMPE患者群では軽度の上昇にとどまることが明らかとなった(平均値はそれぞれ1,543 pg/ml，2,142 pg/ml)(**図3a**)[4]．以上より，急性期の血清TARC値はDIHSとその他の薬疹とを鑑別する有用なバイオマーカーになりうるものと期待される．

DIHSにおける HHV-6再活性化とTARC

臨床的にDIHSが疑われた薬疹患者41症例について，HHV-6再活性化を伴った群(30症例)とHHV-6再活性化を伴わなかった群(11症例)に分けて，急性期のTARC値を比較したところ，HHV-6再活性化群においてTARCが有意に高いことが判明した(**図3b**)[4]．この結果は，TARCの上昇とHHV-6再活性化との間に何らかの関連があることを示している．現時点では推測の域を出ないが，TARCの上昇によりTh2細胞やTregが誘導され，その結果生じた免疫変調がHHV-6再活性化を誘発する可能性や，HHV-6遺伝子上にはヒトのケモカインレセプターホモログ遺伝子がコードされていることから[11]，HHV-6潜伏感染細胞表面に発現しているHHV-6由来のケモカインレセプターにTARCが作用して再活性化を引き起こす可能性などが考えられる．

おわりに

本稿では，血清TARC値がDIHS急性期に著明に上昇することを示し，診断の有力なバイオマーカーとなりうる可能性について述べた．DIHSの診断にはHHV-6再活性化を検出することが大切であるが，現時点では，HHV-6 DNAを測定できる施設は限られており，また，ペア血清を用いた抗HHV-6抗体価による診断は病初期には不可能である．一方，血清TARC値は，HHV-6の再活性化に先んじて上昇し，外注でオーダーすればおおよそ数日で結果が得られる．最近では，17分で結果が出る迅速測定法が普及してきており，DIHSを予測する上で，きわめて有用な迅速検査になりうるものと期待される．現在，血清TARC検査の保険適用が認められているのはアトピー性皮膚炎に限られているが，今後，重症薬疹の診断にも臨床応用可能となることを願っている．

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CONCISE COMMUNICATION

Case of thymoma-associated cutaneous graft-versus-host disease-like disease successfully improved by narrowband ultraviolet B phototherapy

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ABSTRACT

Thymoma-associated graft-versus-host disease (GVHD)-like disease is a rare paraneoplastic disease seen in patients with thymoma. Here, we describe the first case of thymoma-associated GVHD-like disease localized to the skin that was successfully improved by a combination of systemic corticosteroids and whole-body narrowband ultraviolet (UV)-B phototherapy. The patient had developed toxic epidermal necrolysis-like erosive skin lesions over the whole body. Although systemic corticosteroids were effective up to a point, we were unable to begin the steroid taper. The addition of systemic narrowband UV-B phototherapy improved the skin manifestation of this disease, allowing corticosteroids to be reduced to a third of the original dose. Histopathologically, it was confirmed that the proportion of Foxp3-positive lymphocytes in the skin increased after narrowband UV-B irradiation. We propose that whole-body narrowband UV-B phototherapy is a good therapeutic option for the skin manifestation of thymoma-associated GVHD-like disease.

Key words: **Foxp3, graft-versus-host disease, narrowband ultraviolet B phototherapy, paraneoplastic disease, thymoma.**

INTRODUCTION

Thymoma is often associated with a variety of autoimmune diseases such as myasthenia gravis, pure red cell aplasia and thymoma-associated graft-versus-host disease (GVHD)-like disease. Thymoma-associated GVHD-like disease is defined as a disease affecting the liver, intestine or skin. Liver dysfunction, diarrhea and erythema occur in patients with thymoma, and GVHD-like reactions are observed histopathologically in the affected organ. In some cases, a single organ may be affected, and cases in which the disease is only manifested in the skin have been reported in the published work.[1,2]

Because this disease is rare, there exists no consensus on the optimum treatment modality. Although oral corticosteroids or immunosuppressive agents have been tried, it has proven difficult to control this disease. The prognosis is generally unfavorable due to an increased risk of infection-related death.[3] Herein, we report the first case of thymoma-associated cutaneous GVHD-like disease successfully improved by whole-body narrowband UV-B (NBUVB) phototherapy and systemic corticosteroids.

CASE REPORT

A 52-year-old Japanese woman was diagnosed with invasive thymoma at the age of 45 years and developed myasthenia gravis at 48 years. Because thymoma cells had been disseminated to the pericardium in spite of thymectomy, no further treatments could be utilized on admission. One month before her admission, she developed scaly erythema and red papules with itching across the trunk and extremities, which then spread rapidly to the whole body over the course of a few weeks. Topical steroid treatment was ineffective. Several days before admission, she developed fever and widespread epidermal detachment over her whole body. At this point, she was admitted to our hospital. She was treated with tacrolimus (2 mg/day), prednisolone (4 mg/2 days), lansoprazole, minodronic acid hydrate, loxoprofen sodium and morphine sulfate hydrate for over 1 year. On admission, her body temperature was 37.8°C and widespread erythema was observed over her whole body. Widespread epidermal detachment with erythema was observed on the neck, trunk, genital area and extremities,

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involving 30% of her body surface area (Fig. 1a,b). In addition, the patient experienced crusting of the lips and oral mucosal erosion (Fig. 1c). On the upper extremities, flat atypical target lesions were observed (Fig. 1d). She had no gastrointestinal symptoms. Laboratory results, including a complete blood count, renal function and liver enzymes, were almost within the normal ranges, other than elevated C-reactive protein (9.32 mg/dL). Immunoserological examinations showed no evidence of recent infection by mycoplasma, herpes simplex virus 1 or Epstein–Barr virus.

A skin biopsy was performed on the forearm (Fig. 1d). Histopathological examination revealed necrotic changes in the upper epidermis, and moderate infiltration of lymphocytes in the epidermis and upper dermis (Fig. 2a). In the epidermis, numerous apoptotic keratinocytes were observed, accompanied by lymphocytes and satellite cell necrosis. Abundant CD8 T-cell infiltration and a few Foxp3-positive cells were confirmed by immunohistochemistry (Fig. 2b,c). In addition, direct immunofluorescence showed immunoglobulin (Ig)G deposition at the cell surfaces in the epidermis and C3 deposition at both the cell surfaces in the lower layer of the epidermis and the basement membrane zone (Fig. 2d). Because these findings suggested paraneoplastic pemphigus, we further examined the autoantibodies against epidermal components, but indirect immunofluorescence analysis revealed a negative result. Moreover, no anti-desmoglein-1 and -3 antibodies were detected in the patient's serum by enzyme-linked immunosorbent assay. Immunoblot analysis did not detect IgG antibodies for epidermal components including envoplakin and periplakin. Finally, we diagnosed the patient as having thymoma-associated cutaneous GVHD-like disease.

We began the administration of oral 50 mg (1 mg/kg) prednisolone (PSL). The erosion rapidly improved but the erythema, red papules and itching remained. Because we were unable to reduce the dose of PSL for 3 weeks, we tried whole-body NBUVB phototherapy (five times per week, maximum dose 0.72 J/cm^2). The irradiation was performed in a UV 7001 K phototherapy cabinet (Waldmann-Medizintechnik, Villingen-Schwenningen, Germany). The eruption and itching in all areas improved approximately 10 days after starting NBUVB phototherapy, after which we were able to taper PSL to 30 mg (Fig. 3a). After a total NBUVB irradiation of 14.4 J/cm^2, the patient was discharged from our hospital at 10 weeks after admission. In the outpatient department, we continued tapering oral PSL by 1–2.5 mg every month while continuing with NBUVB phototherapy once per week. During the disease course, the patient developed diffuse alopecia; however, this was eventually completely resolved. Up to the present, we have now treated her with oral 14 mg PSL for 7 months. A small amount of itchy erythema has repeatedly appeared over the whole body. A skin biopsy from the erythema on the forearm showed the features of mild interface dermatitis (Fig. 3b). Although the infiltrated CD8 T-cell level was not changed (from 33 ± 5 to 34 ± 5 cells/high-power field [HPF]), significantly more Foxp3-positive cells had infiltrated into the epidermis and dermis as compared with the results of the first skin biopsy (from 3 ± 1 to 24 ± 3 cells/HPF) (Fig. 3c,d). During the disease course, there was no progression of thymoma metastatic lesions and no new metastases.

DISCUSSION

In thymoma-associated GVHD-like disease, various types of cutaneous manifestations have been reported, including keratotic papules, scaly erythema, morbilliform eruptions and erythroderma.[3,4] The most common histological findings are

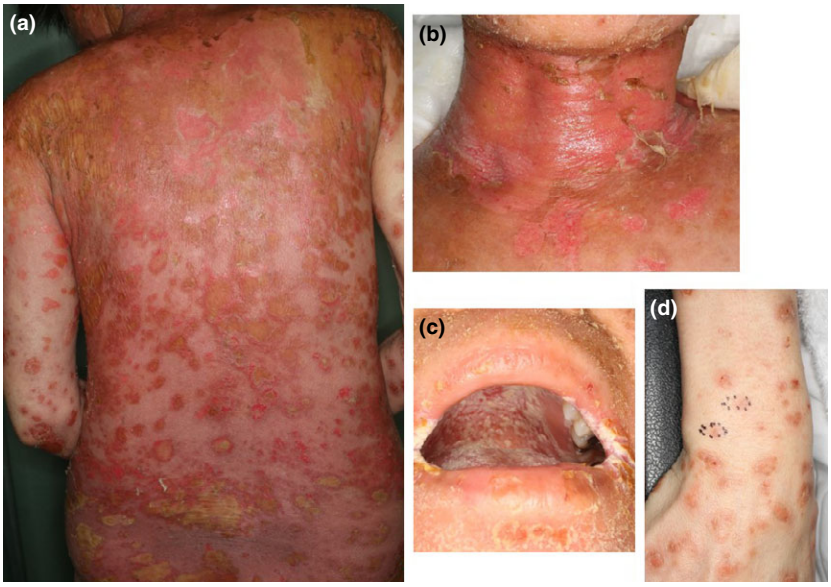

Figure 1. Clinical features on admission. Widespread erythema with (a,b) epidermal detachment and (c) oral mucosal erosions were observed. (d) Skin biopsy was taken from forearm.

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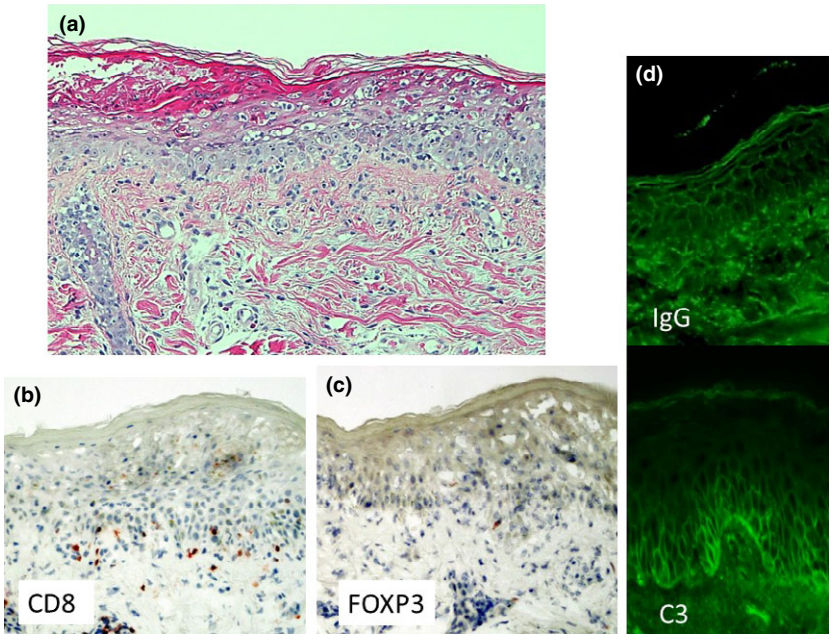

Figure 2. (a) Histopathology showed graft-versus-host disease-like reaction (hematoxylin–eosin, original magnification ×100). Immunohistochemistry showed (b) CD8 T-cell infiltration and (c) few Foxp3 positive cells (×100). (d) Direct immunofluorescence showed immunoglobulin (Ig)G and C3 deposit to the epidermis (×100).

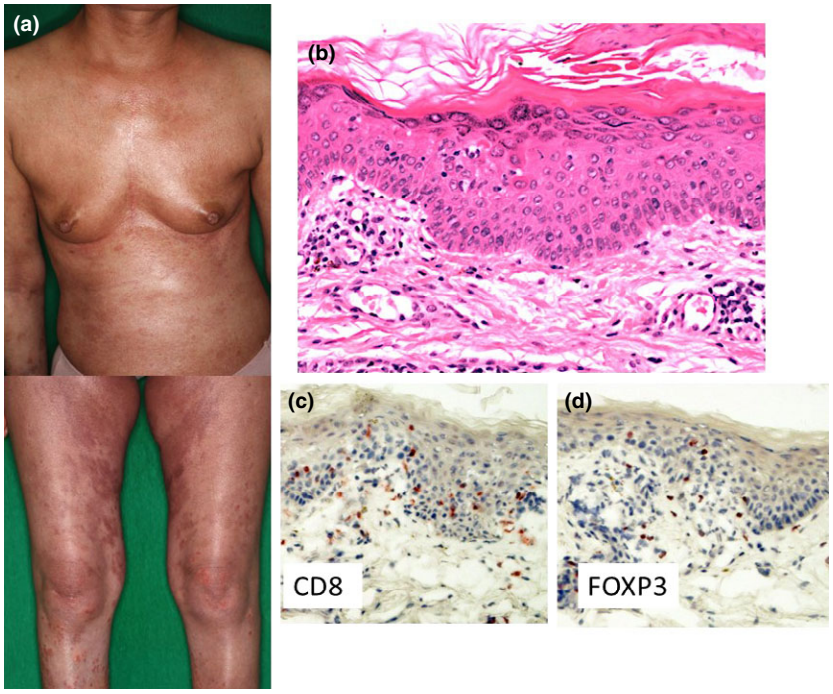

Figure 3. (a) Narrowband ultraviolet B (NBUVB) phototherapy significantly improved the skin manifestations. (b) Although lymphocytes were infiltrated in the epidermis and upper dermis, apoptotic keratinocyte was not observed (hematoxylin–eosin, original magnification ×200). In immunohistochemical analysis, (c) CD8 T cell and (d) Foxp3-positive cells were observed in the epidermis and dermis (×200).

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GVHD-like reactions consisting of liquefaction degeneration and apoptotic keratinocytes accompanied by lymphocytic infiltration in the epidermal layer. It has been demonstrated immunohistopathologically that CD8-positive T cells are dominantly infiltrated in the epidermis, and that the frequency of Foxp3-positive regulatory T cells (Treg) is reduced in the dermis.[5]

In the case of our patient, the skin manifestation resembled toxic epidermal necrolysis, and histopathological findings revealed numerous apoptotic keratinocytes. To the best of our knowledge, no case of thymoma-associated cutaneous GVHD-like disease with toxic epidermal necrolysis-like features has been reported. Paraneoplastic pemphigus, one of the cutaneous complications of thymoma, was excluded because no autoantibodies were detected in the patient's serum. However, because direct immunofluorescence showed the existence of autoantibodies against the intercellular component of the epidermis, it is possible that some kind of autoantibody was involved in facilitating the widespread erosions in this case.

The pathological mechanisms of this disease remain unclear. In the normal thymus, autoreactive T cells are eliminated by apoptosis in a process termed negative selection by medullary thymic epithelial cells (mTEC).[6] This process depends largely on autoimmune regulator (*Aire*) gene expression in mTEC, which controls the ectopic expression of a wide range of peripheral tissue-specific antigens.[5] The lack of *Aire* in thymoma increases the number of autoreactive T cells.[2] Moreover, mTEC plays a critical role in the generation of Treg.[7,8] It is suggested that inadequate T-cell selection and insufficient Treg generation in the tumor environment of the thymus may cause thymoma-associated GVHD-like disease.[5] Because surgical excision of the thymoma and chemotherapy are unable to restore the function of the thymoma cells, systemic corticosteroids and/or immunosuppressive agents such as cyclosporin have been used.[9] However, patients with this disease usually suffer infection-related death due to long-term high-dose immunosuppressive treatments.[3,4] Therefore, the development of an effective treatment is required to improve the prognosis.

Recently, the effectiveness of NBUVB phototherapy for cutaneous GVHD after transplantation has been reported in many cases.[10] The direct effect of NBUVB on lymphocytes infiltrating into the skin is the most plausible mechanism.[11] In addition, it has been demonstrated recently that NBUVB increased the proportion of Treg in GVHD patients' peripheral blood[11] and skin.[12] Based on these findings, we used systemic NBUVB irradiation on our patient. This treatment was effective and allowed us to taper the dose of PSL. In addition, we confirmed that the proportion of Foxp3-positive lymphocytes in the skin was increased after NBUVB irradiation (Figs 2c,3d).

To the best of our knowledge, this is the first reported case of thymoma-associated cutaneous GVHD-like disease successfully treated with systemic NBUVB irradiation. More recently, Nakayama *et al.*[13] reported one case in which targeted NBUVB phototherapy used on a limited area of the lower leg improved the skin eruptions of this disease. Thus, whole-body NBUVB phototherapy may be helpful to allow tapering of the dose of corticosteroids in thymoma-associated cutaneous GVHD-like disease.

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CONFLICT OF INTEREST: None declared.

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2 Stevens-Johnson 症候群

佐山 浩二

高熱，全身倦怠感および重症の粘膜疹を伴い，全身に紅斑・びらん・水疱が多発する疾患である．原因の多くは薬剤である．本症からさらに中毒性表皮壊死症（TEN）へと進展する場合がある．

◎ 診断と検査

診断には「重症多形滲出性紅斑 スティーヴンス・ジョンソン症候群・中毒性表皮壊死症診療ガイドライン」（塩原哲夫ほか，2016）を参考にする．びらん・水疱を伴う汎発性の紅斑，粘膜病変，発熱，病理組織学的な表皮の壊死性変化，erythyma multiforme（EM）major を除外できること，以上5項目が必須である．皮膚病変の面積は10%未満である．皮膚粘膜移行部（眼，口唇，外陰部など）には広範囲で重篤な粘膜病変（出血・血痂を伴うびらんなど）がみられる．EM major において粘膜疹は口唇の発赤腫脹，わずかなびらん程度である．また，自己免疫性水疱症を除外する必要がある．

病理組織検査では全層性の表皮壊死がみられるが，検査時期により壊死の程度は異なる．200倍視野で10個以上の表皮細胞死を確認することが望ましい．

原因薬剤としては抗菌薬，解熱鎮痛薬，抗けいれん薬が多い．原因薬剤検索のために薬剤誘発性リンパ球刺激試験（DLST）を行う．急性期に陽性となり，回復後は陰性となることが多い．感染症を原因として疑う場合はマイコプラズマ抗体価を検査する．

白血球数・分画の測定に加えて，肝・腎機能検査，呼吸器障害を疑う場合は胸部X線撮影，CT，血液ガス検査を行う．また，副腎皮質ステロイド（ステロイド）投与に際して感染症や糖尿病のチェックも必要である．

◎ 治療の一般方針

1 治療方針の立て方

治療の原則は原因薬剤の中止，ステロイドの全身投与である．また，口腔内の疼痛のため摂食障害を伴うので補液・栄養管理による全身管理が必要である．ステロイドで十分な効果が得られない場合，ステロイドパルス療法，免疫グロブリン大量静注療法，血漿交換療法などの併用を検討する．眼では偽膜形成や眼表面上皮欠損がみられ，視力障害やドライアイなど重篤な後遺症を残すため眼科受診が必要である．

2 全身療法

プレドニゾロン換算で中等症は0.5～1 mg/kg/日，重症は1～2 mg/kg/日で開始する．効果がみられたら3～7日ごとにプレドニゾロン換算で10 mg/日程度減量する．十分な効果が得られない場合ステロイドパルス療法としてメチルプレドニゾロン500～1,000 mg/日を3日間投与する．パルス療法直後はプレドニゾロン換算で1～2 mg/kg/日を投与し，効果がみられたら漸減する．免疫グロブリン大量静注療法ではヒト免疫グロブリン製剤400 mg/kg/日を5日間連続投与する．

3 外用療法

びらん，水疱部位の処置は熱傷に準じて行う．微温湯で洗浄後，軟膏や創傷被覆材などで保護する．眼病変に対しては眼科指示によりステロイド，抗菌薬を用いる．

◎ 処方例

①プレドニゾロン（5 mg）：12錠，分2，朝夕
②白色ワセリン：100 g，1日1回ガーゼに塗布し病変部を保護

◎ 生活指導

薬剤が原因の場合は薬疹カードを渡し再投与されないように指導する．薬疹の場合は医薬品副作用被害救済制度が利用できること，また薬疹以外の場合でも重症多形滲出性紅斑として特定疾患に認定されているため公費負担の対象となることを説明する．

トピックス

国内では薬事承認されていないがシクロスポリンの有用性も報告されている．71例のSJS/TEN患者のうち，15例のシクロスポリン（3～5 mg/kg/日，平均7日間）投与患者と35例のヒト免疫グロブリン製剤使用例とを比較したところ，シクロスポリン投与例で死亡率が低かった．
Kirchhof MG et al : J Am Acad Dermatol 71 : 941, 2014

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REVIEW ARTICLE

Immune reconstitution inflammatory syndrome in non-HIV immunosuppressed patients

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ABSTRACT

Immune reconstitution inflammatory syndrome (IRIS) represents a clinical phenomenon of immune-mediated inflammation against various antigens, including pathogenic microorganisms, drugs and unknown autoantigens, during recovery from immunosuppressed conditions. IRIS has become well recognized in HIV-infected populations. However, IRIS has seldom been recognized in HIV-negative immunocompromised patients. In the last 15 years, the immunopathogenesis of drug-induced hypersensitivity syndrome (DIHS) has been largely determined. Laboratory data and clinical observations support the idea that DIHS represents a prototype of non-HIV IRIS. Primary diseases in which non-HIV IRIS is secondary include severe cutaneous adverse drug reactions, such as DIHS, autoimmune diseases, collagen diseases, pregnancy and internal malignancies. Potential triggers of recovery from an immune deterioration state include a discontinuation or abrupt tapering of systemic steroids and/or immunosuppressants, withdrawal or reduced effects of anti-tumor necrosis factor-α antibodies, and the use of immune-checkpoint antagonists for the advanced stages of malignancies. Wide use of IRIS across large populations risks oversimplification but highlights a key unifying principle. Balanced sensitivity and specificity for its diagnostic criteria and classification are necessary for the establishment of clinical practice guidelines for non-HIV IRIS. Additionally, the development of a useful combination of biomarkers is currently an urgent issue.

Key words: anti-tumor necrosis factor-α antibodies, drug-induced hypersensitivity syndrome, immune-checkpoint antagonists, non-HIV immune reconstitution inflammatory syndrome, systemic steroid.

INTRODUCTION

Immune reconstitution inflammatory syndrome (IRIS) constitutes a group of diseases that develop or become exacerbated when the immune response recovers following antiretroviral therapy (ART) for HIV infection.[1] Diagnostic criteria for IRIS were formulated in 2006. IRIS occurs in 10–25% of unselected patients starting ART and approximately 52–78% of these cases involve cutaneous lesions.[2] Among patients not infected with HIV, immune reconstitution can occur even if the temporary use of immunosuppressive agents is terminated.[3] However, IRIS has seldom been recognized in patients other than those infected with HIV.[4,5] A small number of case reports regarding the paradoxical response during the chemotherapy of tuberculosis have been published since 1987.[6] In the last 10 years, we have found that p.o. administration of certain drugs (especially anticonvulsants) for 2–6 weeks triggers immunosuppression and cessation of such therapy provokes the reactivation of various viruses, including Epstein–Barr virus (EBV), human herpes virus (HHV)-6 and cytomegalovirus (CMV), similar to IRIS.[7,8] The diseases that develop include liver disorders, pneumonia, enteritis, encephalitis, pandemic shingles, fulminant type 1 diabetes and chronic thyroiditis.[9,10] We have established diagnostic criteria and treatment guidelines for the condition, which we refer to as drug-induced hypersensitivity syndrome (DIHS).[11]

In recent years, many novel drugs with immunological actions have been developed; these complement "conventional" immunosuppressants. The new drugs principally target malignant tumors and autoimmune diseases. Various immune-related adverse events (irAE) have been described,[12] many of which are common with sequelae of DIHS and events following ART; thus, these adverse events can be regarded as IRIS.

If immunosuppressive agents are stopped or reduced abruptly, immune reconstitution will be accelerated, possibly exacerbating adverse events. Furthermore, simple discontinuation of an effective treatment is most disadvantageous to patients. It is thus urgent to establish and disseminate an expanded concept of IRIS. Establishment of the concept, a definition and diagnostic criteria for non-HIV IRIS will aid clinical decision-making about whether to continue treatment of the original disease, including autoimmune conditions and malignant tumors, and will guide appropriate treatment of adverse events.

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DRAFT DIAGNOSTIC CRITERIA AND POSSIBLE BIOMARKERS

Non-HIV IRIS is defined broadly in HIV-negative patients as inflammatory events in various organs against antigens or pathogenic microorganisms assumed to have existed prior to recovery from the immune deterioration state. These inflammatory events manifest within a few months (unmasking) and/or are exacerbations of inflammatory events that had already developed or were treated before immune reconstitution (paradoxical). Exclusion criteria include: (i) exacerbation of the primary disease within the assumption, despite appropriate treatment; (ii) relapse/exacerbation of the primary disease due to withdrawal of effective treatment of the underlying diseases; and (iii) inflammatory events due to newly ingested antigens or pathogenic microorganisms following recovery from the immunocompromised state (Table 1). More than half of HIV-associated IRIS cases present with cutaneous manifestations.[2] Skin symptoms are also common in non-HIV IRIS. Because the degree of immune suppression in non-HIV IRIS is generally milder than that in HIV IRIS, the immune recovery curve is also not as abrupt. Given this, there is an opinion that the term "immune reconstitution" is not appropriate. More recently, HIV infections have been identified and treated at earlier time points than previously. As a result, IRIS patients exhibiting a steep recovery from advanced immunodeficiency are decreasing markedly.

A schematic of non-HIV IRIS is shown in Figure 1. Primary diseases in which non-HIV IRIS is secondary include severe cutaneous adverse drug reactions, such as DIHS, autoimmune diseases, collagen diseases, pregnancy and internal malignancies, including cancers, lymphoma/leukemia and sarcoma. Potential triggers of recovery from an immune deterioration state include discontinuation or abrupt tapering of systemic steroids and/or immunosuppressants, withdrawal or reduced effects of biologics, including anti-tumor necrosis factor (TNF)-α antibodies, and the use of immune-checkpoint antagonists for advanced stages of malignancies. Typical examples of unmasking IRIS are manifested CMV infection and herpes zoster, while those of paradoxical IRIS include the exacerbation of tuberculosis and non-tuberculous mycobacteriosis, triggered by the withdrawal of anti-TNF-α antibodies or immunosuppressive agents. Manifestation of type 1 diabetes mellitus, thyroiditis, hepatitis, interstitial pneumonia, sarcoidosis, psoriasiform and lichenoid eruption, and other drug eruptions are also seen with non-HIV IRIS. These non-infectious IRIS diseases could be a result of inflammatory processes reacting with known or unknown autoantigens or exogenous antigens, including pharmacological agents.

The timing of occurrence regarding IRIS events is highly variable depending on each infectious and non-infectious disease. The timing of herpes zoster, the most common manifestation of IRIS in HIV-infected patients, also varies. However, in 50% of cases, the onset of herpes zoster occurred within the first 4 weeks after the initiation of ART.[13] HIV-negative patients receiving immunosuppressive agents including corticosteroids and chemotherapies for cancers have an increased risk of herpes zoster as a manifestation of IRIS. In a case series, most cancer patients developed herpes zoster 1–3 months after the final course of chemotherapy, while patients with rheumatoid arthritis (RA) or lupus erythematosus developed herpes zoster 1–3 weeks after tapering the dose of oral prednisolone.[14] In most HIV-negative patients with herpes zoster occurring upon the withdrawal or reduction of immunosuppressants, skin lesions appear on the trunk and extremities, but not on the face and head. Although our case series of DIHS was not large enough to draw definitive conclusions on the interval at which IRIS events occur after the onset of DIHS, CMV infections occurred within a month, most herpes zoster within 6 months, fulminant type 1 diabetes between 1 and 2 months, autoimmune thyroiditis between 2 months and 3 years, alopecia and vitiligo at 4 months, and systemic lupus erythematosus (SLE) at 3.5 years.[9,10] Hence, most autoimmune diseases emerged later than infectious diseases during the long course of DIHS.

Immune reconstitution inflammatory syndrome is characterized by an innate and adaptive immune response to different

Table 1. Draft diagnostic criteria

Concept
We studied the clinical courses of inflammatory disorders of various organs triggered by pre-existing antigens and pathogenic microorganisms. We included disorders that developed over several months, those that had recently manifested and those that were already being treated but that clearly worsened upon recovery of HIV-negative patients from immunocompromised conditions.
Essential criteria (required)
1. HIV-negative.
2. The disorder was associated with recovery from an immunocompromised condition.
3. (i) The inflammatory disorder was caused by an antigen (including a drug) or a pathogenic microorganism present prior to immune recovery (unmasking); or (ii) exacerbation of an inflammatory disorder that had already developed or was being treated (a paradoxical disorder); or both (i) and (ii).
Exclusion criteria
1. Exacerbation of primary disease after appropriate treatment.
2. Relapse/exacerbation of primary disease attributable to withdrawal of effective treatment.
3. An inflammatory disorder attributable to a newly ingested antigen or pathogenic microorganism after recovery from the immunocompromised condition.
Supportive findings
1. Multiple inflammatory disorders may develop simultaneously or sequentially.
2. Primary diseases include severe cutaneous adverse drug reactions such as drug-induced hypersensitivity syndrome; autoimmune, collagen and related diseases; malignant tumors; and pregnancy.
Diagnosis: If a condition met all inclusion and exclusion criteria, that condition was considered to be non-HIV immune reconstitution inflammatory syndrome.

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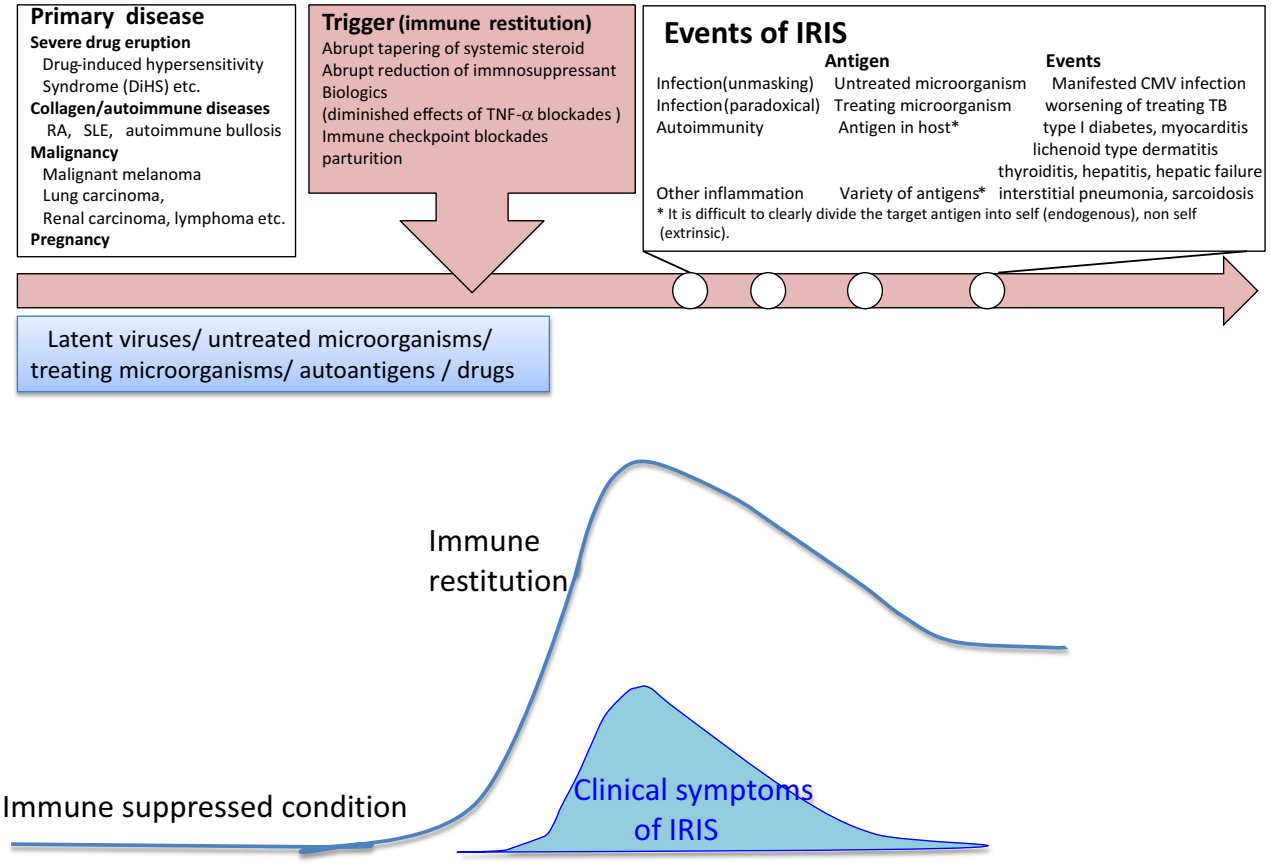

Figure 1. Schematic representing the concept of immune reconstitution inflammatory syndrome (IRIS). Primary diseases in which non-HIV IRIS can occur, potential triggers of the recovery from the immune deterioration state and corresponding IRIS events are illustrated. CMV, cytomegalovirus; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TB, tuberculosis; TNF, tumor necrosis factor.

antigens, leading to the release of cytokines and chemokines. The cytokines and chemokines may differ, depending on the type of antigen; for example, interferon (IFN)-γ, interleukin (IL)-2, IL-6, TNF-α and IFN-γ-inducible protein (IP)-10 in *Mycobacterium tuberculosis*-associated IRIS.[15,16] Another group demonstrated significantly elevated concentrations of IL-10 and IL-22 in tuberculosis-associated IRIS patients compared with those in non-IRIS patients with tuberculosis.[17] Cerebrospinal fluid levels of pro-inflammatory cytokines such as IFN-γ, TNF-α, granulocyte colony-stimulating factor, vascular endothelial growth factor and eotaxin (CCL11) were increased significantly from baseline in patients with cryptococcal meningitis-associated IRIS but not in patients with cryptococcal meningitis relapse.[18] The same group reported that pre-ART increases in IL-17 and IL-4 and a lack of pro-inflammatory cytokine responses predisposed individuals to the subsequent development of cryptococcal meningitis and served as serum biomarkers of IRIS.[19] Increased IL-8, T-helper (Th)1 and Th17 cytokine levels in HIV IRIS patients precede ART initiation and could help identify patient populations at higher risk for IRIS.[20] Biomarkers of non-HIV IRIS have not yet been established. Possible predictors of non-HIV IRIS events identified to date include C-reactive protein, IL-6, IL-8, IL-10, IL-17, IP-10 and IFN-γ.[13,20]

DRUG ERUPTIONS AND NON-HIV IRIS

In the dermatological field, non-HIV IRIS has attracted attention as a result of determining the pathogenesis of DIHS. One of the most remarkable features of DIHS is the paradoxical deterioration in clinical status, such as high fever and skin rash, frequent relapse and the step-wise development of severe organ failure, despite withdrawal of the causative drug.[21] In many cases of DIHS, several herpes viruses, including HHV-6, HHV-7, EBV and CMV, can be reactivated during the course of this syndrome in a sequential order, similar to graft-versus-host disease (GVHD).[8] The mechanisms of reactivation of these viruses have not been fully examined. Immature monocytes in which HHV-6 is latent circulate in the blood and are trafficked into the skin and infect $CD4^+$ T cells over the course of DIHS.[22] It has also been hypothesized that reactivation of HHV-6 could occur prior to activation of drug antigen-specific T cells at an

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early time point.[21] At the onset of DIHS, withdrawal of the causative drug induces rapid restoration of immunity and reduces viral loads, thereby rendering them undetectable in the blood in early DIHS. More rarely, CMV infections manifesting gastritis, enterocolitis, pneumonia and skin lesions, such as ulcers, vesicles and prurigo-like lesions, can occur as events of IRIS during the course of DIHS.[23] Monitoring of CMV reactivation is necessary to improve the potentially fatal course of CMV infection. We conducted a follow-up survey of 145 patients with DIHS following recovery from the acute stage.[10] There were nine cases of autoimmune thyroiditis, five cases each of fulminant type 1 diabetes mellitus and herpes zoster, two cases each of arthritis and pneumonia, and one case each of alopecia, SLE and vitiligo.[10] Most of these diseases are similar to those that occur in HIV IRIS. In the diagnostic criteria of HIV IRIS proposed by Shelburne *et al.*,[1] an increase in $CD4^+$ T-cell numbers is a prerequisite for the diagnosis of IRIS. In nine out of 10 cases of DIHS, $CD4^+$ T-cell numbers increased initially and then declined gradually, reaching normal values by 2 months after onset.[7] The changes in lymphocyte subsets were observed with or without systemic corticosteroid administration.[7] Additionally, the degree of increase in $CD4^+$ T-cell numbers correlated with the severity of clinical symptoms of DIHS, including the extent of rashes. Patients with DIHS at the acute stage showed significantly increased frequencies of regulatory T cells (Treg) in total $CD4^+$ T cells compared with healthy controls, which declined following resolution.[11] In addition, dysfunction of Treg at resolution could contribute to the exacerbation of pre-existing infection and/or autoimmunity that often ensues. Treg contracted upon resolution of DIHS gradually became functionally deficient.[24] In contrast, the frequency of Treg is low in both the acute and resolution periods of toxic epidermal necrolysis (TEN).[24] Functional defects of Treg in TEN were transitory and restored upon recovery. Thus, the risk of subsequently developing events was minimized.[24] These observations collectively support the idea that DIHS represents a prototype of non-HIV IRIS.

PREGNANCY/PARTURITION AND NON-HIV IRIS

Pregnancy is a state of subtle immunosuppression, characterized by physiological suppression of pro-inflammatory host responses that promote tolerance to fetal antigens, thus contributing to a healthy gestation.[25,26] In a normal human pregnancy, an increase in circulating Treg during early pregnancy, peaking during the second trimester and then a decline post-partum, has been reported.[27] An increase in the number of Treg may be important in maintaining maternofetal tolerance.[28] The Th17/Treg balance is important for maternal tolerance to the fetus while still fighting any infection. Local immunoreactivity at the maternal–fetal interface also shifts towards Th2; however, a return to a Th1-dominant response in the post-partum period may increase the inflammatory response to an underlying infection or exacerbate autoimmune diseases.[29] Tuberculosis during pregnancy was associated with extrapulmonary infection in 5–10% of patients, whereas 93% of patients with tuberculosis during the post-partum period had tuberculosis with extrapulmonary involvement and, surprisingly, 69% of these patients had a central nervous system infection.[30] Autoimmune disorders, such as RA, SLE and multiple sclerosis (MS), are often characterized by a disturbed Th17/Treg balance that results in increased levels of pathogenic Th17 cells, associated with reduced Treg numbers and activity.[31] Autoimmune diseases dominated by inflammatory immune responses, such as RA and MS, reportedly improve during late pregnancy but worsen after parturition. Indeed, two studies have suggested an association between the increased number of Treg and the improvement in RA disease activity in pregnancy.[31]

Psoriasis is a common chronic inflammatory skin disease. It remains controversial as to whether psoriasis is a primary autoimmune disease or secondarily evolves into autoimmunity, as seen in other chronic inflammatory diseases. Murase *et al.*[32] examined 47 pregnant patients with psoriasis and how psoriasis fluctuated in pregnancy and post-partum. During pregnancy, 55% of the patients improved, 21% reported no change and 23% worsened. However, post-partum, only 9% of patients reported improvement, 26% reported no change and 65% reported worsening. Psoriatic body surface area (BSA) decreased significantly from 10 to 20 weeks' gestation ($P < 0.001$) compared with controls, whereas BSA increased significantly by 6 weeks post-partum ($P = 0.001$) compared with controls. In patients with 10% or greater psoriatic BSA who reported improvement ($n = 16$; mean BSA, 40%), lesions decreased by 83.8% during pregnancy. There were significant or near-significant correlations between improvement in BSA and estradiol ($P = 0.009$, $r = 0.648$), estriol ($P = 0.06$, $r = 0.491$) and the ratio of estrogen to progesterone ($P = 0.006$, $r = 0.671$).[32] In psoriasis, it has been suggested that the decreased Th17/Treg ratio, due to expansion of Treg during pregnancy, leads to the improvement of symptoms and the reduction in Treg after parturition contributes to the deterioration of symptoms.[31] That is, the Th2 cytokine-mediated down-regulation of the immune response, by virtue of its anti-inflammatory and antagonizing effects on the Th1 cytokines, improves psoriasis during pregnancy.[33]

Breast-feeding significantly influences the epidemiology of postnatal human CMV infection.[34] Of the 69 seronegative breast-feeding control mothers, none had detectable CMV DNA in breast milk and none of their 80 infants shed the virus in urine. In contrast, 73 of 76 seropositive breast-feeding mothers demonstrated CMV DNA in breast milk and 33 infants shed CMV in the urine.[35] Breast-feeding is a source of postnatal CMV infection in preterm infants. The mean post-partum days for the appearance of CMV DNA in breast milk was 3.5 days in transmitters to infants, but 8 days in non-transmitters ($P = 0.025$). The copy numbers of CMV DNA in breast milk increased rapidly, peaked at 3–5 weeks post-partum and then declined.[35] These findings may be explained partly by immune reconstitution due to the decreased number and function of Treg post-partum. The correlation of CMV reactivation and transition of Treg has also been studied in GVHD.[36,37] The number of Treg was lower in patients with than without CMV infection and/or GVHD at 2 ($P < 0.001$) and 3 months

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($P < 0.001$) after allogeneic peripheral blood stem cell transplantation.[36] Moreover, a positive correlation was found between the number of Treg and the recovery of CMV-specific $CD8^+$ T cells at 2 ($P < 0.0001$, $r = 0.61$) and 3 months ($P < 0.00001$, $r = 0.72$).[36] In a subsequent study, a reduced proportion of $CD4^+$ $CD25^{high}$ $FOXP3^+$ Treg in total lymphocytes was reported in patients with CMV viremia at day 30 after stem cell transplantation.[37]

IMMUNE-RELATED ADVERSE EVENTS BY CHECKPOINT BLOCKADE

Anti-programmed cell death protein 1 (PD-1) antibodies, nivolumab and pembrolizumab, the anti-PDL1 antibody avelumab, and the anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody ipilimumab, which target T-cell checkpoint receptors in the treatment of advanced melanoma and/or Merkel cell carcinoma, have produced impressive effects in the dermatological field.[38] Opportunities for these immunotherapies are increasing because they have demonstrated significant efficacy against lung cancer and have also been used against other cancers.[39] In patients treated concurrently with ipilimumab and nivolumab, approximately 50% developed grade 3/4 irAE,[40] compared with patients treated with either nivolumab (<14%)[38]or ipilimumab (<20%) alone.[41] IrAE occur due to therapy-associated release of cytokines, such as IFN-γ and TNF-α, and infiltration of activated and proliferating effector T cells in different organs.[38] IrAE due to immune-checkpoint blockades are also consistent with the concept of non-HIV IRIS, because recovery and enhancement from an immunocompromised state due to advanced cancer and/or anticancer drugs is their central pathogenesis. IrAE occasionally encountered include enterocolitis, hepatitis, dermatitis, neuropathy, endocrinopathies and interstitial pneumonia, while those rarely reported include uveitis, diabetes mellitus, pancreatitis, nephritis, Guillain–Barré syndrome and demyelinating diseases.[39,42,43] Cutaneous adverse events are frequent and show early onset, within several weeks, during CTLA-4 and/or PD-1 therapy. Physical examination shows reticular, maculopapular or erythematous rashes on the extremities or trunk.[44] Lichenoid or psoriasiform eruptions are rarely encountered. Oral mucositis and/or complaints of dry mouth have been reported in a small percentage of patients.[45] Most cutaneous adverse events are not severe and immune-checkpoint blockades can be continued. Extremely infrequently, severe adverse reactions, such as Stevens–Johnson syndrome and TEN, have been reported. Interestingly, there are many common immune-mediated events between irAE by checkpoint blockades and extracutaneous diseases merging or following the acute period of DIHS (Table 2). Various infectious diseases can occur during the treatment of malignancies with checkpoint blockades[46] as well as DIHS. Thus, differential diagnosis with infectious disease is important for the treatment and management of irAE.[38]

In humans, increased Treg numbers and proportions have been associated with worse prognosis in some cancers, because Treg suppress antitumor immunity by inhibiting the effector function of immune cells.[47] Both PD-1 and CTLA-4 blockades have been shown to attenuate the suppressive effects of Treg.[48] These data suggest that the efficacy of immune-checkpoint inhibitors and their irAE may be attributed to the depletion and altered function of Treg.[49,50] Immunological mechanisms of irAE and DIHS can be explained similarly by the transition of Treg; hence, both conditions can be broadly considered within the concept of non-HIV IRIS.

Table 2. Comparison of irAE and events following DIHS

irAE due to immune checkpoint blockades	Events following the DIHS
Diarrhea, enterocolitis	Gastrointestinal bleeding
Gastrointestinal bleeding	Hepatitis, hepatic dysfunction
Hepatitis, fulminant hepatitis	Alopecia
Pancreatitis	Nephritis, renal dysfunction
Nephritis	Interstitial pneumonia/pneumonia
Interstitial pneumonia	Dermatitis, drug rash
Dermatitis, drug rash	Herpes zoster, herpes simplex
Rheumatoid arthritis	Cryptococcus pneumonia
Thyroid dysfunction	Pneumocystis carinii pneumonia
Hypophysitis	Thyroid dysfunction/thyroiditis
Encephalitis	Encephalitis/limbic encephalitis
Myocarditis	Myocarditis
Type 1 diabetes mellitus	Type 1 diabetes mellitus
Adrenal failure	
Vasculitis	
Sarcoidosis	
Myasthenia gravis	
Vitiligo	

Underlined events are common in both independent diseases. DIHS, drug-induced hypersensitivity syndrome; irAE, immune-related adverse events.

PARADOXICAL RESPONSE DURING TREATMENT BY TNF-α BLOCKADES

Tumor necrosis factor-α inhibitors, such as infliximab and adalimumab, have been used widely for patients with psoriasis vulgaris, pustular psoriasis and psoriatic arthritis in dermatology.[51] Exacerbations of pre-existing or masking infections, such as tuberculosis,[52] and autoimmune diseases, such as SLE, polymyositis and autoimmune blistering disease, have been recognized after cessation or secondary invalidation of TNF-α inhibitors. These events can be understood as a paradoxical response or IRIS.[53] Little is known about the immunological pathogenesis of these responses. Tuberculosis infections associated with TNF-α inhibitors tend to demonstrate unusual clinical manifestations with acute onset. For example, lung tuberculosis shows high fever and strong respiratory symptoms, mimicking bacterial pneumonia and disseminated small nodules on chest X rays.[54]

An atypical manifestation of cutaneous tuberculosis that resembles bacterial cellulitis has been reported 3 months after starting infliximab.[55] These atypical manifestations of tuberculosis occasionally developed in patients with HIV infection receiving ART. The acute cellulitis-like inflammation might have

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resulted from recovery of immune responses against latent *M. tuberculosis* that were suppressed during the TNF-α blockade.[56] A lethal case of disseminated tuberculosis after discontinuation of adalimumab because of invalidation in a patient with synovitis, acne, pustulosis, hyperostosis and osteitis syndrome has been reported, in whom paradoxical events occurred concurrently with the elevation of circulating TNF-α and a decline in IFN-γ levels.[57] If tuberculosis is found during anti-TNF-α therapy, then the anti-TNF-α agent should not be withdrawn because it may lead to severe tuberculosis. TNF-α inhibitors also induce psoriasiform rashes as an adverse event in patients with Crohn's disease and RA. However, patients who discontinued TNF-α blockades also had the greatest resolution of psoriasiform rashes, compared with those who switched to different anti-TNF agents or continued the previous therapy. These outcomes are not explained by the concept of IRIS. It is necessary to examine differences between groups that suffer IRIS events and a group that does not due to TNF-α inhibitor invalidation or discontinuation.

MANAGEMENT OF NON-HIV IRIS

Therapeutic guidelines for non-HIV IRIS have not yet been established. One of the possible advantages of recognizing the concept of non-HIV-type IRIS, we believe, is that physicians would not hesitate to use immunosuppressants, even in the setting of opportunistic infections. Corticosteroids are the most frequently employed agent, based on clinical trial data in HIV-infected patients.[58] Because a mild case of IRIS responds to specific treatment for the underlying pathogens, anti-inflammatory therapies are not generally required. TNF-α inhibitors[57] and anti-IL-6 antibodies can be treatment options for patients with non-HIV IRIS. Recently, statins have attracted attention as immunomodulators and anti-inflammatory agents in the management of GVHD. Statins promote the development of Th2 and Treg, inhibit pro-inflammatory Th1-driven responses and block Th17 cell development.[59] A protective effect of statins against infection and sepsis has been reported.[60] Thus, statins have potential for the treatment of non-HIV IRIS. Maintaining a balance between host immunity and infectious microorganisms is essential in the management of non-HIV-type IRIS. When pathogenic microorganisms are obvious, primary antimicrobial agents are basically necessary in most cases, but not all cases, depending on the nature of the pathogen, its mechanism of immunological defense and the severity of clinical manifestation. For example, CMV infection during immunosuppressive therapy with manifestation of visceral involvement is generally treated by antivirals together with previously used immunosuppressive agents, whereas antivirals may be unnecessary for CMV reactivation without obvious clinical manifestations.

CONCLUSIONS AND FUTURE DIRECTIONS

Establishment of the concept, definition and diagnostic criteria of non-HIV-type IRIS will aid clinical decision-making about whether to continue treatment of the original disease, including autoimmune conditions and malignant tumors, and will guide the appropriate treatment of adverse events. We believe that this new concept will benefit patients. Establishment of clinical practice guidelines and the development of a useful combination of biomarkers are urgent issues for the future.

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CONFLICT OF INTEREST: None declared.

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