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CASE REPORT

Severe type of erythema multiforme (EM major) due to administration of Anti-PD-1 antibody drug

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ABSTRACT

Immune checkpoint inhibitors can sometimes cause unexpected skin side effects. Special attention should be paid to a severe form of erythema multiforme (EM), toxic epidermal necrolysis and Stevens-Johnson syndrome. We experienced a patient who took 10 weeks from drug discontinuation to the onset of EM major.

Keywords: Immune Checkpoint Inhibitors; Immune-related Adverse Events; Erythema Multiforme; Erythema Multiforme Major

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1. Introduction

Immune checkpoint inhibitors (ICI) have radically changed the treatment of several cancers[1]. Of note, in addition to an increased anti-tumor immunity, the mechanism of action of ICIs reveals a new toxicity profile called immune-related adverse events (irAEs)[2,3]. All organs can be affected by these new toxicities, although the more frefrequently affected organs include the skin, digestive, and endocrine or- gans[3,4]. The majority of toxicities caused by ICIs are low in severity, but some are more serious and require multidisciplinary management of side effects[5]. In the case of skin, a severe form of erythema multiforme, toxic epidermal necrolysis and Stevens-Johnson syndrome are very serious, and diagnosis and treatment are frequently difficult. Recently we encountered a case with a severe type of erythema multiforme (EM major) due to administration of anti-PD-1 antibody drug, who showed a unique clinical course. Herein this case is reported.

2. Case presentation

Two years before the first visit to our department, an 80-year-old Japanese man had been aware of fatigue and shortness of breath during exertion, and visited the department of respiratory medicine in Takatsuki Red Cross Hospital, Osaka, Japan. His past history included chronic obstructive pulmonary diseases and type II diabetes. Upon closer examination, he was diagnosed as lung adenocarcinoma stage IV (multiple metastases in lymph nodes, multiple rib and iliac). Chemotherapy with carboplatin and pemetrexed was started, and one year before the first visit, the improvement of lung, multiple lymph nodes, and multiple rib/iliac metastases was observed, but renal function was

deteriorated, so the procedure was completed in 5 courses. Six months later, metastasis progressed, and an anti-PD-1 antibody drug (pembrolizumab) was administered. Pembrolizumab was discontinued after 6 courses due to drug-induced lung disorder. The administration of pembrolizumab was discontinued and the patient was followed up, but 10 weeks after the discontinuation of the administration, erythematous lesions with pruritus appeared on the face and neck. Topical corticosteroids were used, but the skin lesions spread throughout the body 2 days later, and he was refered to our department for detailed examination and treatment.

At the first visit, body temperature was 37°C and there was no hyperemia in the bulbar conjunctiva. He had erosive lesions on lips. Coin-sized erythema was scattered on the face, auricle, and neck (**Figure 1**). The back of the abdomen and limbs were scattered with coin-sized erythema with the infiltration, and some of them tended to heal. Fused atypical erythematous lesions were seen throughout the body (**Figure 2**).

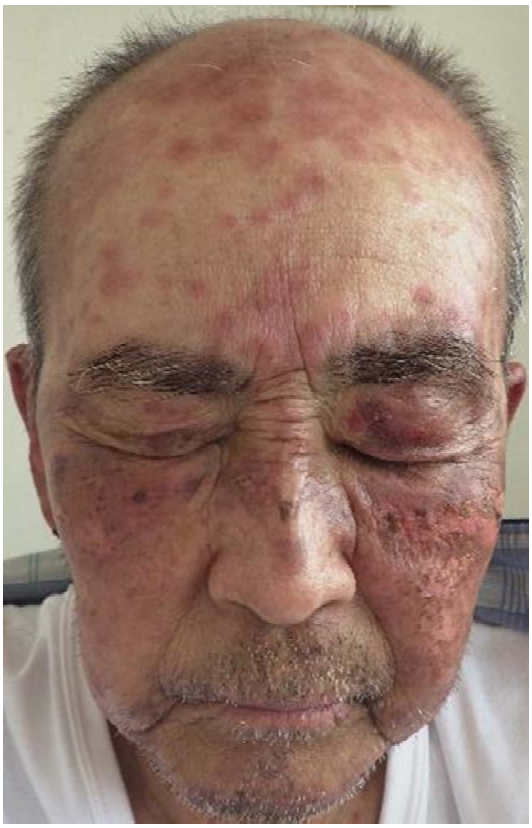

Figure 1. The patient had erosive lesions on lips, and coin-sized erythema was scattered on the face, auricle, and neck**.**

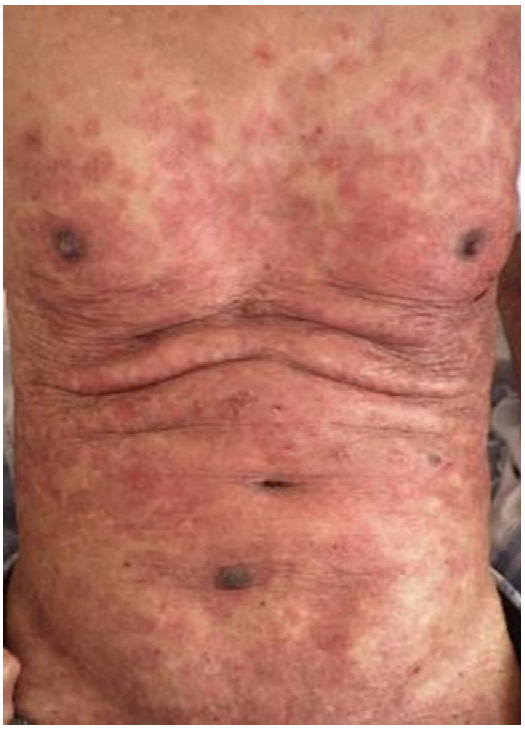

Figure 2. Coin-sized erythematous lesions with the infiltration and fused atypical lesions were seen throughout the body**.**

Blood test findings at the first visit. No increase in eosinophils or liver enzymes was observed. Considering the possibility of bullous pemphigoid and pemphigus vulgaris, anti-desmoglein antibodies and anti-BP180 antibody were measured, but they were within the standard values.

A skin biopsy, it was obtained from the abdominal lesion. There are vacuolar degeneration and individual cell necrosis at the epidermal-dermis junction. Infiltration of inflammatory cells (mainly lymphocytes) around the superficial blood vessels of the dermis (**Figure 3**).

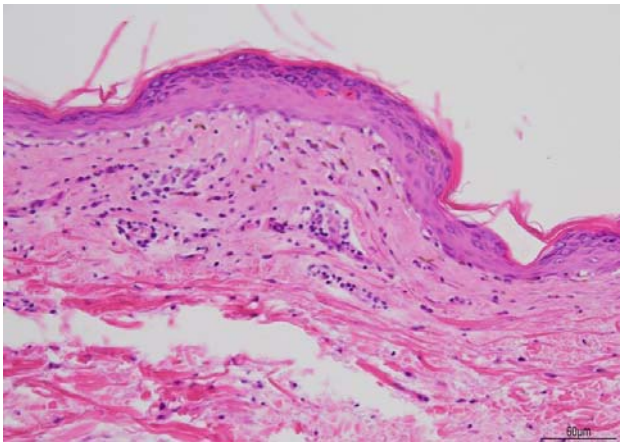

Figure 3. Pathological findings revealed vacuolar degeneration and individual cell necrosis at the epidermal-dermis junction (x200)**.**

Possibility of drug eruption other than pem-

brolizumab was considered and the possible drugs that caused EM major were discontinued. Although PSL was 0.5 mg/kg/day was administered, the skin lesions expanded. Based on the pathological finding and clinical lesions such as the increased severity, erythematous lesions located in the extremities and mild mucosal lesions, we diagnosed EM major.

Due to drug-induced lung injury, 6 cools pembrolizumab were completed and 10 weeks had passed. Initially, considering drug eruption other than pembrolizumab, possible agents discontinued such as magnesium oxide tablets, eszopiclone, lansoprazole enteric coated tablets, sulfamethoxazole/trimethoprim tablets, and PSL 0.5 mg / kg started. However, the eruption expanded and erosion of the lips also appeared. Considering irAEs of pembrolizumab, the dose was increased to 1 mg/kg of PSL, and the eruption was improved and the PSL was gradually decreased (**Figure 4**).

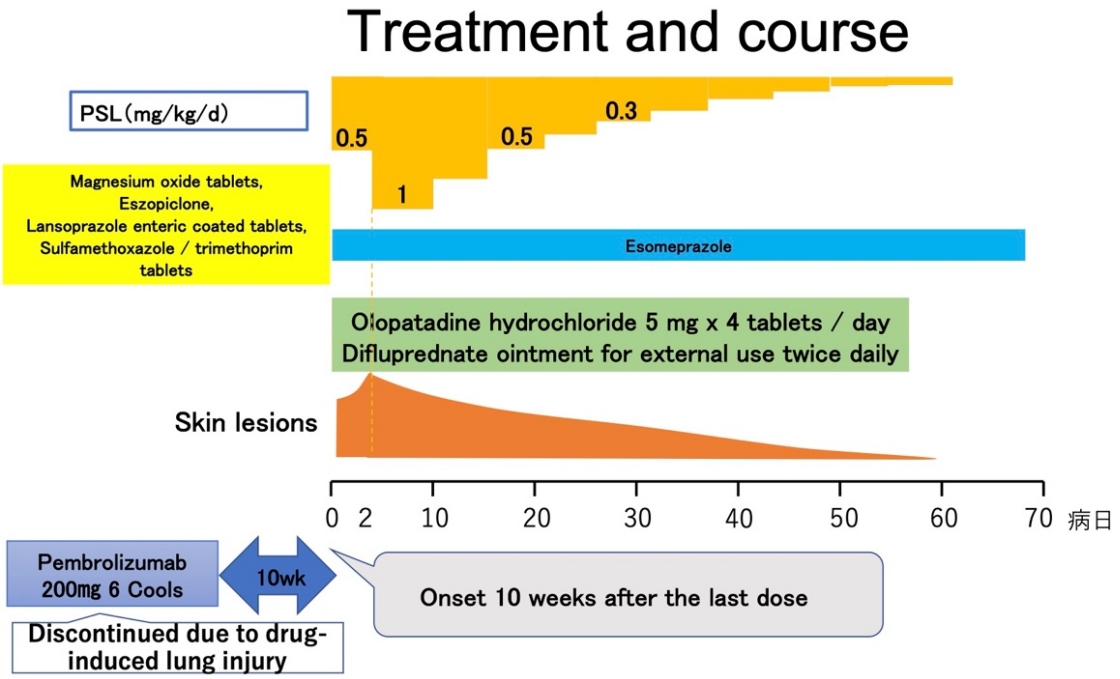

Figure 4. Treatment and course.

3. Discussion

The majority of toxicities caused by ICIs are low in severity, but some are more serious and require multidisciplinary management of side effects. To reduce the risk of experiencing severe toxicities, gathering information on different immune toxicities has been necessary and treatment practices have needed to adapt quickly[3, 5].

Side effects of irAE are different from conventional drugs[3, 4]. For examples, all organs can be injured and the passage or course of time is also various. There are many reports including skin disorders, digestive disorders (colitis, diarrhea), interstitial lung disease, myasthenia gravis, myocarditis, rhabdomyolysis, neuropathy, liver dysfunction, kidney disorder, encephalitis, endocrine disorders (Type I diabetes, thyroid dysfunction, adrenal insufficiency, hypophysitis) and so on. The incidence of skin disorders is 17-35%, such as mild form of erythematous papules, toxic epidermal necrolysis, Stevens-Johnson syndrome, psoriasis-like rash, lichen-like rash, autoimmune bullous disease, etc[6,7]. Recent report indicated that the most prevalent dermatological toxicities were alopecia (27%), pruritus, and rash (10%). Remarkably, the prevalent severity was graded 1−2 for both alopecia, pruritus and rash[6].

In the present case, a rash appeared 10 weeks after the end of anti-PD-1 antibody administration. In cases reported in Japan, the longest period from the end of anti-PD-1 antibody administration to the appearance of eruption was 8 weeks[8]. When examining patients during or after administration of ICIs, it is important to keep in mind that severe mucocutaneous disorders can occur regardless of the

duration of the last dose[9,10]. In addition, dermatological treatments and skin care must be tailored to the patient's condition[5,11].

Conflict of interest disclosure

None declared.

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COMMENTARY

Effects of immune checkpoint inhibitors on cancer patients with pre-existing autoimmune disease

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Keywords: Immune Checkpoint Inhibitors; Malignant Melanoma; Cancer; Immune-related Adverse Events; Pre-existing Autoimmune Disease

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Since immune checkpoint inhibitors (ICIs) imbalance the immune system, this drug causes a secondary autoimmune condition[1-3]. Then on the contrary, it is a very interesting question whether they can be used in cancer patients with autoimmune diseases or what side effects they cause.

The Netherlands study group reported that response rates for ICIs in patients with advanced melanoma are comparable with or without pre-existing autoimmune disease (PAD) such as rheumatologic PAD, endocrine PAD, inflammatory bowel disease (IBD) PAD, or others[4]. Among patients with coexisting autoimmune diseases when receiving anti-CTLA-4 therapy, anti-PD-1 therapy, or a combination of both, the incidence of grade 3 or higher new toxicity profile called immune-related adverse events (irAEs) occurred in 30%, 17%, and 44%, respectively. In patients with non-autoimmune diseases, it was 30%, 13% and 48%, respectively. Compared to non-autoimmune diseases, patients with autoimmune diseases were more likely to discontinue anti-PD-1 therapy due to toxicity. Anti-PD-1-induced colitis was common in patients with IBD. Patients who received anti-CTLA-4, anti-PD-1, and combination therapy had similar objective response rates in autoimmune diseases and non-autoimmune diseases patients. So, taken together, the authors concluded that there was no difference in survival with or without autoimmune diseases.

Based on the meta-analysis of observational studies and nationwide multicenter cohort study[5,6], immune toxicities are frequent in ICI-treated patients with PAD but often mild and manageable without discontinuing therapy. It was concluded that ICI treatments are also effective in PAD patients although immunosuppressive therapies at baseline are associated with poorer outcomes.

At present, ICI may be used in cancer patients with autoimmune diseases. It should be noted that many of the reported cases are rheumatoid arthritis (RA). Risks and benefits should be considered with special cares and attentions for multi-organ autoimmune diseases and/or collagen diseases such as systemic lupus erythematosus, which has different mechanisms from RA.

Conflict of interest disclosure

None declared.

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REVIEW ARTICLE

Hydroxychloroquine for the treatment of cutaneous lupus erythematosus

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Running title: Hydroxychloroquine for cutaneous lupus erythematosus

ABSTRACT

In recent years of immunology, the understanding of innate immunity has deepened, and the concept of innate immunity has been proposed even in the area of acquired immune subjects. The conventional immunosuppressive treatments have mainly controlled the step of acquired immunity. However, the involvement of innate immunity was clarified for hydroxychloroquine (HCQ), which has been confirmed to be very effective for cutaneous lupus erythematosus (CLE). This review introduces the mechanism of development of CLE from the viewpoint of autoantibodies, cytokines, and innate immunity. Furthermore, the mechanism of HCQ is introduced and discussed.

Keywords: Hydroxychloroquine; Innate Immunity; Cutaneous Lupus Erythematosus; Systemic Lupus Erythematosus; Treatment; COVID-19

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1. Introduction

Hydroxychloroquine sulfate (HCQ) is the world standard treatment for cutaneous lupus erythematosus (CLE) and systemic LE (SLE). In Japan, HCQ could not be administered due to the frequent appearance of severe side effects for a long time[1]. It was later discovered that the high frequency of severe side effects was due to the wrong administration method.

The Japan Hydroxychloroquine Study Group was established with Drs. Furukawa F, Yokogawa N and Yamamoto K as the main members, and several case reports were published[2,3]. Furthermore, the usefulness of HCQ was confirmed in autoimmune-prone MRL/l mice with skin lesions[4,5]. In 2017, a multicenter, double-blind, randomized, parallel-group trial in Japan reported effectiveness of HCQ in patients with CLE[6]. About a year and a half before this publication, HCQ could be used in Japan for the treatment of CLE and SLE from September 2015, which was officially approved by the Japanese Ministry of Health, Labor and Welfare. Furthermore, since this drug sometimes causes serious side effects such as retinal degeneration, a guide for proper use has also been published[7]. In addition, HCQ was reported to be effective against the new coronavirus infection (COVID-19), so it attracted a lot of attention[8].

This paper introduces clinical trials on HCQ characteristics, usage for CLE, clinical effects, precautions for use, side effects, etc.

2. Mechanism of onset of skin lupus erythematosus from the viewpoint of innate immunity

Well-known mechanisms include the involvement of antibody-dependent cellular cytotoxicity (ADCC) targeting SS-A/Ro antigens[9,10,11] and the cytokine and/or chemokine network model described below[12,13].

2.1 From the perspective of autoantibodies

The serological feature of SLE is the presence of autoantibodies. It is still hard to say that the role of anti-DNA antibodies is elucidated in skin lesions, except for their involvement in renal lesions. On the other hand, it became clear from clinical and research aspects that there is a strong relationship between photosensitivity of subacute CLE (SCLE) and neonatal LE (NLE) and serum anti-SS-A/Ro antibody. It has become a research model for photosensitivity[9,10]. A typical model is ADCC, which targets SS-A/Ro antigens. When cultured epidermal cells derived from normal adult or neonatal foreskin are irradiated with ultraviolet light B (UVB), the antigen is translocated and up-regulated on the cell surface, and anti-60 kD/Ro antibody and anti-52 kD/Ro antibody are bound to induce ADCC. A similar tendency is observed in cultured epidermal cells derived from patients[9].

The mechanism by which autoantibodies move into cells and bind to the corresponding antigens has been a problem/question, but the movement of the antigen due to stimuli such as UV lights (UVLs) causes binding[14]. It was important that the antigen moved to the surface, not the antibody. This phenomenon is induced not only by UVLs but also by changes in temperature and external factors such as under heat shock protein induction[11] (See **Figure 1**).

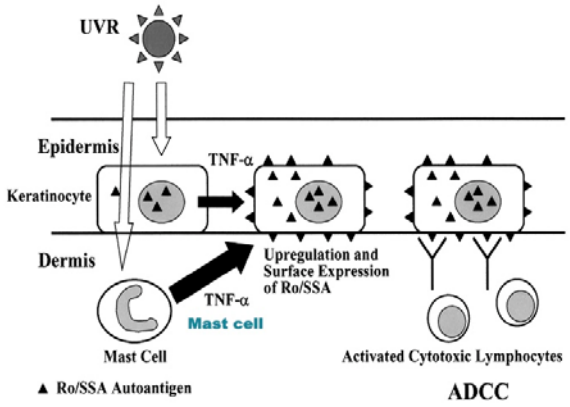

Figure 1. Ultraviolet radiation (UVR) induces antibody dependent cellular cytotoxicity (ADCC) model targeting SS-A/Ro antigen which is mediated by transfer necrosis factor (TNF) α from mast cells (10,11,14).

2.2 From the viewpoint of cytokines

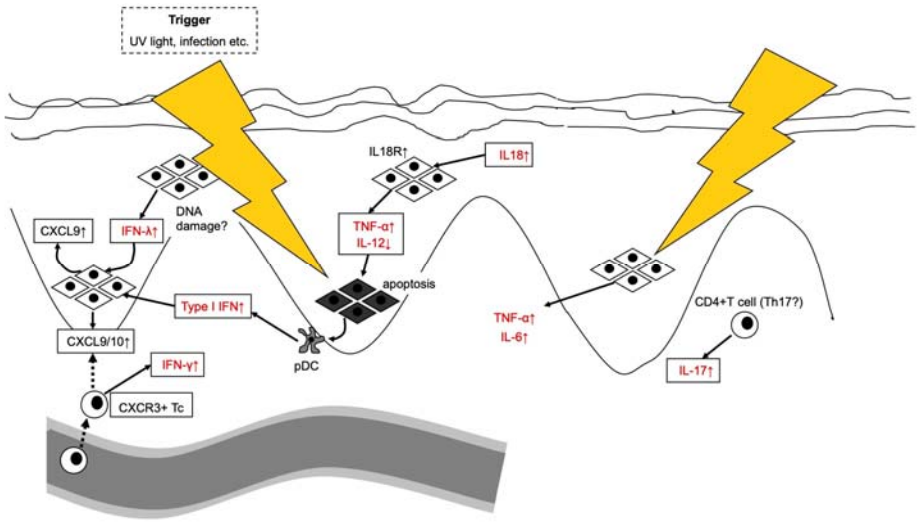

Figure 2. Involvement of cytokines in CLE (Mikita's model).

Discoid LE (DLE), which is a typical disease of chronic CLE (CCLE), has an antinuclear antibody positive rate of about 50%. The rate of disease specific autoantibody is extremely low, and no ADCC is

observed. However, because eruptions often occur in sun-exposed areas and characteristic skin lesions from clinical and pathological features, DLE patients have a different mechanism from the pathogenesis of acute CLE (ACLE)) in SLE patients[15,16]. Cytokines such as TNFα and IL-12 and infiltrating cells have been shown to be important in photosensitivity. The same applies not only to DLE but also to LE (mainly CCLE) that does not have disease-specific autoantibodies (See **Figure 2**).

2.3 Involvement of innate immunity

In recent years of immunology, the understanding of innate immunity has deepened, and at the same time, the concept of innate immunity has been proposed even in the area of acquired immune subjects[17].

Wenzel proposed an innate immunity-acquired immune cycle model in CLE onset[18]. Genetic predisposition including IFN regulation, antigen presentation, and immune complex removal, first exists and then involvement of environmental factors such as UVLs, tobacco, and drugs begins to drive the unbalanced immune cycle. Then the loop cycle begins to rotate for completion of CLE, in which several mechanisms are involved such as innate immunity (IFN activation, inflammatory cytokine production, activation of complement system activetion), acquired immunity (activation of cytotoxic cells, antigen presentation, autoantibody production), histological completion of skin lesions and amplification of auto-reaction phenomenon (release of nucleic acid components, activation of keratinocytes, activation of pDC, etc.).

This concept clarified and made it easier to understand the relationship with treatment methods involved in immunity. The conventional immunosuppressive treatments have mainly controlled the step of acquired immunity in systemic treatments. A recent paper by Sim *et al.*[19] has the interpretation from a similar new perspective. In addition, Nakajo Nishimura Syndrome suggests the involvement of autoinflammation in the development of LE-like lesions[20,21,22].

3. Action mechanisms of hydroxychloroquine

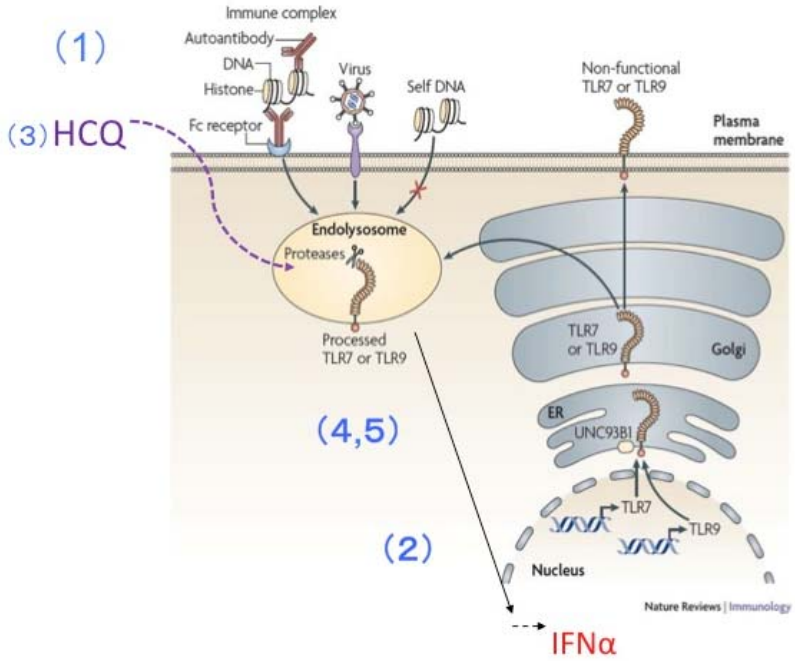

Figure 3. Possible mechanism of action of HCQ (There are some modifications by the author, from ref. 24)**.** (1) Nucleic acids that are continuously present in excess are processed by dendritic cells as autoantigens. (2) IFNα overproduction mediated by TLR7, 9. (3) Administration of HCQ. (4) Positively charged and accumulated in lysosomes to change pH and inhibits the step 2. (5) Then it inhibits the immune response to self-antigens, but does not impair the response to foreign antigens, so it exhibits immunomodulatory effects without immunosuppression.

HCQ is an old and new drug. It has a long history of use, and it is only recently that one of its mechanisms has been clarified from the perspective of immunity[23]. This drug has a wide range of ac-

tions such as anti-inflammatory action, immunomodulatory action, antimalarial action, and antitumor action. Although multiple mechanisms of action have been proposed, basic studies of innate immunity have revealed an inhibitory effect on innate immune disorders.

In SLE, excess apoptosis cell-derived nucleic acids are expected to form and stabilize immune complexes with autoantibodies and to be persistently presented. They are processed by dendritic cells and binds to Toll-like receptors 7 and 9 in lysosomes, resulting in overproduction of IFNα. HCQ accumulates in lysosomes, changes pH, and inhibits Toll-like receptor-mediated IFNα production and dendritic cell maturation. This mechanism has no immunosuppressive effect and exhibits an immunomodulatory effect[24] (**Figure 3**). HCQ is understood to have excellent therapeutic effects by controlling the first step in Wenzel cycle[18]: innate immunity, such as IFN activation, inflammatory cytokine production, and complement system activation.

4. What kind of patients are targets?

1) For CLE patients with only localized skin symptoms, when topical preparations such as corticosteroids are inadequately effective or when the use of external preparations is inappropriate.

2) For SLE patients in whom skin lesions exist including malaise, musculoskeletal symptoms, etc.

(These are cited from reference 7 that was published for Japanese physicians)

5. Clinical data evidence and problems of hydroxychloroquine

For Japanese patients diagnosed with CLE with or without SLE, 200 to 400 mg of this drug (not to exceed 6.5 mg/kg in ideal body weight) is orally administered once daily for efficacy and safety. As described in our previous reports[6,7], HCQ was found to be effective against active skin lesions. In SLE patients, RAPID3 (daily life activity, muscle or joint pain due to primary disease [VAS], severity due to primary disease evaluated by patients [VAS]), and malaise VAS were all statistically significant for improvement 16 weeks after administration in the HCQ group[6].

According to a recent post-marketing surveillance (September 7, 2015 - April 18, 2020), the efficacy rates for skin lesions in 331 patients after 16 and 52 weeks were 41.7% and 49.9%, respectively. Side effects were observed in 159 cases (15.8%) out of 1007 cases subject to safety analysis, and serious side effects appeared in 17 cases (1.7%). From almost the same analysis, serious side effects included 6 severe skin disorders (2 cases of erythema multiforme and 4 cases of toxic derma or eruption) and 4 cases of eye disorders (posterior capsule opacity, retinal pigment epithelium, retinopathy, and retinal pigment epithelial detachment)[25]. In terms of frequency of occurrence, drug eruption and rash are the most common, followed by diarrhea and other gastrointestinal symptoms.

A systematic review by Sharma *et al.*[26] revealed that drug eruption or rash (358 cases) was the most common, and hyperpigmentation of the skin (116 cases), pruritus (62 cases), and acute generalized exanthematous pusutulosis or -like disease (27 cases), Stevens-Johnson syndrome or toxic epidermal necrolysis (26 cases), hair loss (12 cases), and stomatitis (11 cases) have been reported. The nomenclature of skin lesions is not always unified in the world. Most of the drug eruptions developed within 4 weeks after the start of HCQ administration and disappeared within a few weeks after discontinuation. It is not necessary to decrease or discontinue for patients with drug eruption up to moderate diseases that do not other organs' problems[27,28].

Retinal degeneration is the most notable side effect of HCQ. Petri M *et al.* states that it is important to monitor the blood concentration of HCQ[29], but since the onset of retinopathy of HCQ involves multiple factors including genetic background such as race, and the significance of blood concentration, it will be investigated in the future[30,31, 32].

6. Trends and future prospects in the treatments of CLE

Regarding HCQ, the algorithms suitable for Japanese or Asian people was proposed who still

have some restrictions on drugs to be administered[6,33], but there are many important issues to be clarified such as the selection of the type of skin lesions for which HCQ is effective or not[2,34,35], effects of combination therapy[36,37] and more sensitive and early diagnostic methods for retinal degeneration[29,30,31,32].

On the other hand, due to the limited number of treatments for CLE, several new drugs are being developed. Some recent trials are introduced[37]. BIIB059 is an antibody that targets IFN, and Anifrolumab is also an antibody against type I interferon receptor, both of which have been excellently reported in the interim report. Iberdomide is positioned as an immunomodulator and exerts its medicinal effect by binding to cereblon (CRBN), which is a component of the substrate receptor[38]. With the launch of these new drugs, great expectations are placed on the wide range of treatment options.

Appendix

HCQ was taken up as a treatment for the pandemic new coronavirus in the early stages of exploring treatments. There is a background that HCQ also has an antiviral effect against the coronavirus that causes emerging infectious diseases[8]. It has been found to have in vitro activity against SARS-CoV-2 and had come to be mainly used in the United States as a drug expected to be effective against COVID-19, but its efficacy was not determined. Recent papers or reports denied the usefulness of HCQ to COVID-19[39].

Conflict of interest disclosure

None declared

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MINI-REVIEW

Pathomechanism of malignant melanoma

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ABSTRACT

Treatment of malignant melanoma has made great strides in the last decade. On the one hand, immune checkpoint inhibitors and molecular targeted drugs improved the prognosis of patients. On the other hand, it is very important to be aware of the causes of malignant melanoma based on the latest knowledge. In this review, I will briefly review the carcinogenic mechanism of malignant melanoma from the aspects of ultraviolet rays, mechanical stress, trauma and so on.

Keywords: Malignant Melanoma; Mutation; Ultraviolet Ray; Pathomechanism

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1. Introduction

The treatment of malignant melanoma has changed significantly with the launch of immune checkpoint inhibitors[1,2]. There are also reports on appropriate drug therapy[3] and measures against side effects, and safer and more effective treatment methods are being pursued[4-6]. For that purpose, it is necessary to update the cause of malignant melanoma.

Ultraviolet light (UVL) is the oldest and most well-known cause of malignant melanoma. It is widely known that the incidence of malignant melanoma is significantly higher in Caucasians than in colored races including Asians, and awareness-raising activities for UV protection are currently being actively carried out, especially in Europe and the United States. Recently, it has been pointed out that external force, trauma, radiation, etc. may also trigger malignant melanoma.

In this paper, I would like to outline the causes or triggers of these malignant melanomas, including some basic data.

2. UV rays and malignant melanoma

In the living body, when exposed to UV rays, pyrimidine dimers (**Figure 1**) and 6-4 photoproducts (**Figure 2**) are produced[7], and the mutation of cytosine to thymine (CT mutation) occurs, if repair systems do not work (**Figure 3**).

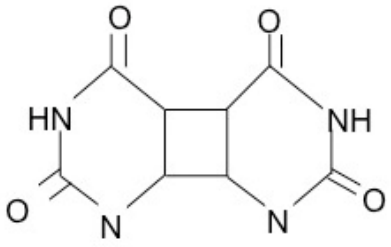

Figure 1. Pyrimidine dimer produced by ultraviolet rays.

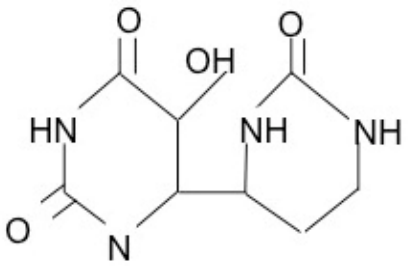

Figure 2. 6-4 photoproducts produced by ultraviolet rays**.**

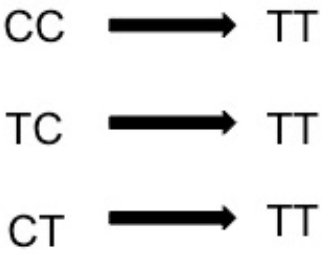

Figure 3. Cytosine to thymine mutation caused by ultraviolet rays (CT mutation)**.**

Normally, when pyrimidine dimer or 6-4 photoproduct is produced, UV-specific endonuclease recognizes and incises DNA, DNA polymerase replicates DNA from the normal side, DNA ligase implants, and repair is completed.

A disease in which UV repair function is congenitally impaired is xeroderma pigmentosum (XP), which is an autosomal recessive inheritance disease. Patients with XP develop erythema when exposed to solar UV rays from an early age, and often develop malignant melanoma, squamous cell carcinoma (SCC), basal cell carcinoma (BCC), etc. at an early age.

Among UV rays, medium-wave UVB (ultraviolet B) has been considered to have a strong carcinogenic effect, but recently, it has become clear that long-wave UVA (ultraviolet A) is also involved in carcinogenesis. Skin cancer is more likely to occur in exposed areas than in non-exposed areas, and within the same ethnic group, the incidence is higher in the equatorial region where the sun's rays are stronger. In addition, skin cancer occurs more frequently in people working outdoors than indoors, and the risk of skin cancer is inversely correlated with the degree of melanin pigmentation. From these results, it is considered that solar UV rays are deeply involved in skin malignant tumors such as SCC, BCC, and malignant melanoma, and the number of patients with any skin malignant tumor increased due to ozone layer depletion.

Malignant melanoma often occurs in exposed areas in Europe and the United States, and it is thought that UV rays are involved. In Japan, the number of cases is high in the southern regions in terms of latitude, in which the primary site is 14% on the face and head, and 27% on the sole, which does not necessarily occur on the exposed area. It is speculated that the number of acral types will increase because the amount of melanin in the skin of the yellow race is larger than Caucasian and its protective ability is associated with relative low number of UV-induced malignant even if the number of cases is the same.

3. Model animal for malignant mela-noma

In 1989, Setlow *et al.*[8] exposed zebrafish to visible light to make the first model animal for malignant melanoma. In 2002, Noonan *et al.*[9] succeeded to develop malignant melanoma in the epidermis of irradiate hepatocyte growth factor (HGF) transgenic mice with UVB + UVA at 3, 5, and 6 weeks after birth.

In 1998, Kunisada *et al.*[10] linked c-kit under the keratin 14 promoter to overexpress stem cell factor (SCF) in the epidermis, and created transgenic mice with mast cell proliferation and melanocytes present in the epidermis. By crossing this mouse with an XPA knockout mouse, a mouse having high UV sensitivity and having melanocytes in the epidermis was created[11]. In this mouse, when a large amount of UVB was irradiated, malignant melanoma could be generated in the epidermis even when it was not a child, and it became a mouse model closer to human malignant melanoma.

Thus, these results suggest that UV rays are essentially involved in the development of malignant melanoma.

4. Foot sole melanoma and mecha-nical stress

As mentioned above, it has become clear that UV rays are closely related to the development of malignant melanoma, but malignant melanoma does not always occur in exposed areas, and factors other

than UV rays are also involved. The sole of the foot is a common site for malignant melanoma in Japanese as well as Asian people, in which the amount of UV exposure is low. The effects of mechanical stress on sole malignant melanoma were investigated at Shinshu University, Japan[12].

Of the malignant melanomas treated at Shinshu University, Japan from 1990 to 2014, 123 cases with lesions on the sole of the foot were included, and cases originating from the nails were excluded. Detailed lesion locations were compared using clinical photographs, and resected specimens measured tumor thickness on a Breslow scale. Of the 123 cases, 54 were male and 69 were female, with an average age of 73.5 years. It occurred on the left sole in 61 cases and on the right sole in 62 cases. The number of lesions by tumor thickness on the Breslow scale was 28 for in situ, 12 for 1 mm or less, 20 for 1.01 mm to 2 mm, 28 for 2.01 mm to 4 mm, 33 for 4.01 mm or more, and 2 for unmeasurable. Analysis of mapping the center of the lesions revealed that the most lesions were distributed in the heel, followed by the 1st and 5th toes. In addition, there were almost no lesions on the arch. There was no bias in the distribution of lesions depending on the tumor thickness. Looking at the number of lesions per 1 cm^2, many lesions were accumulated in the heel and toe, but there were almost no lesions in the arch. From these facts, it was speculated that mechanical stress due to load-bearing was involved in the pathophysiology of sole malignant melanoma.

5. Trauma and subungual malignant melanoma

There is a history of trauma in subungual malignant melanoma, and there are many cases in which trauma may be the trigger. According to the report by Takai *et al.*[13], 62% of all subungual malignant melanomas were accompanied by obvious trauma. Omoto *et al.*[14] collected the literature on subungal malignant melanoma with a history of trauma, and the average time from trauma to diagnosis was 99 months for adults and children. For those who develop pigmented streaks as a result of trauma and subsequently develop malignant melanoma, the average time to diagnosis is about 130 months for adults and 72 months for children. Besides, it has been reported that the time to onset of pigmented streaks with trauma is as short as 15 months in adults, and that it progresses rapidly after trauma in children.

In other words, subungual malignant melanoma appears earlier when trauma is applied to the part where the pigmented streak was originally present than where there is no pigmented streak.

6. Radiation and malignant melanoma

Otsu *et al.*[15] reported the proportion of cutaneous malignancies that developed after irradiation for 1923-1980 and 1981-2014, which were collected from Japanese literatures mainly. In 1923-1980, 62% had SCC, 12.6% had BCC, 3.7% had intraepidermal cancer including Bowen's disease, and 0% had malignant melanoma. As well, in 1981-2014, 42% had SCC, 29.4% had BCC, 7.5% had intraepidermal cancer including Bowen's disease, and 2.5% had malignant melanoma. That is, the proportion of BCC has markedly increased in recent years. The reason for this is that radiation was used for benign skin diseases including tumor diseases and chronic inflammatory diseases previously. The relative decrease in SCC was due to the improvement of site selection, irradiating dose reduction, and tangential irradiation application. Radiation-induced malignant melanoma is extremely rare compared to SCC, BCC, and Bowen's disease, whether or not the slight increase of 2.5% makes sense.

7. AID and malignant melanoma

AID is an activation-induced cytidine deaminase (activation induced deaminase), a 24- kDa enzyme that removes an amino group from a cytidine group in DNA. In 2000, it was shown that this AID is essential for immunoglobulin class switching and point mutations in the variable region of immunoglobulin[16].

Moreover, it was hypothesized that AID is highly expressed in various malignant tumors such as liver cancer and gastric cancer, and that AID is induced by various inflammations and infections.

Furthermore, the induction of a point mutation is speculated to be closely associated with carcinogenesis. When the expression of AID was examined in malignant melanoma, it was revealed that malignant melanoma with high expression of AID frequently causes $BRAF^{V600E}$ mutation and has a poor prognosis[17].

In addition, malignant melanoma spontaneously developed when AID was highly expressed in all organs under the promoter that expresses it in all organs[18]. From these reports, AID may be involved in the development of $BRAF^{V600E}$ mutation and malignant melanoma.

Conflict of interest disclosure

None declared.

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CASE REPORT

Psoriasis in an Asian patient with atopic dermatitis treated with dupilumab

Running title: Psoriasis during dupilumab therapy

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ABSTRACT

Dupilumab is a monoclonal antibody against the alpha subunit of the interleukin (IL)-4 receptor that inhibits IL-4 and IL-13 signaling, which plays a central role in Th2 inflammation in AD.

Here, we report the first Asian case of psoriasis unexpectedly induced by dupilumab therapy for AD. Compared with European and American AD phenotype, Asian AD phenotype is characterized by changes in the psoriasiform phenotype, associating with higher Th17 activation. The blockade of IL-4/IL-13 signaling by dupilumab may induce psoriasis eruption corresponding to shift from a Th2- to Th17- mediated inflammatory response in the skin.

Keywords: Dupilumab; Atopic Dermatitis; Psoriasis; Th2; Th17

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1. Introduction

Asian patients with atopic dermatitis (AD) present a blended phenotype between that of European and American patients with AD and those with psoriasis, establishing consistent Th17/Th2 inflammation(1).

Dupilumab is a monoclonal antibody against the alpha subunit of the interleukin (IL)-4 receptor that inhibits IL-4 and IL-13 signaling, which plays a central role in Th2 inflammation in AD(2). Here, we report the first Asian case of psoriasis unexpectedly induced by dupilumab therapy for AD.

2. Case presentation

A 52-year-old Japanese man who had been diagnosed with AD in childhood was started on dupilumab therapy. He had no personal or family history of psoriasis. He was previously treated with oral prednisolone (10 mg/day) and topical steroids, but his skin symptoms were not well controlled, and he developed erythematous patches with indistinct borders on his chest, abdomen, and face (Eczema Area and Severity Index [EASI] 30) (**Figure 1(a)**). A skin biopsy of the erythema on the abdomen showed mild spongiosis and hyperkeratosis infiltrated with lymphocytes and eosinophils (**Figure 1(b)**). Serum total IgE and thymus and activation-regulated chemokine (TARC) levels were elevated to 12761.5 IU/mL and 1018 pg/mL, respectively. Shortly after dupilumab initiation, the severe itchiness dramatically reduced, and his skin lesions also improved (EASI 13.2 at 3 months). After 8 months of

treatment with dupilumab, serum total IgE levels and TARC decreased to 1405 IU/mL and 329 pg/mL, respectively, but the patient developed well-demarcated and raised plaques with coarse surfaces on the scalp, forehead, and buttocks (**Figure 1(c), (d)**). The morphology of the lesions was highly suggestive of psoriasis. Skin biopsy from the hyperkeratotic plaque on the buttock showed a para-keratotic scale, regular elongation of the rete ridges, and dilation of the vessels in the papillary dermis infiltrated with lymphocytes and eosinophils (**Figure 1(e)**). We diagnosed the patient with dupilumab-induced psoriasis, and discontinued dupilumab therapy and initiated treatment with topical steroids and vitamin D analogues. One month after the discontinuation of dupilumab, scaling on the head cleared and hyperkeratotic plaques on the buttocks gradually reduced.

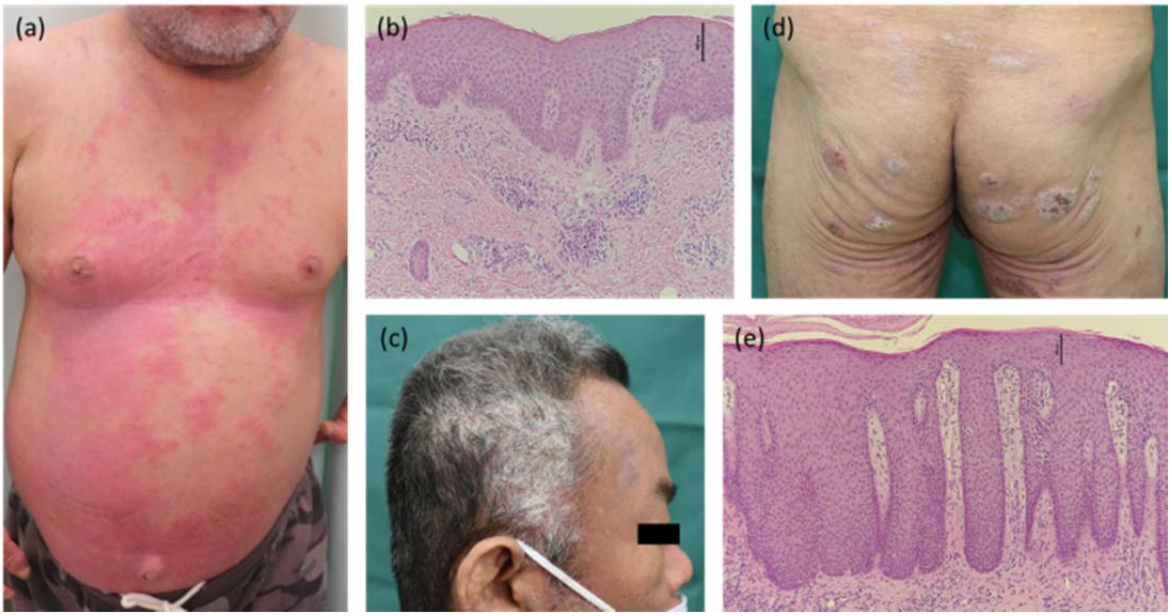

Figure 1. (a) Abdominal erythema before dupilumab treatment. **(b)** Skin biopsy from the erythema on the abdomen showed mild spongiosis and hyperkeratosis infiltrated with lymphocytes and eosinophils (Scale bar shows 100 μm). Eight months after the initiation of dupilumab treatment, psoriatic plaques have developed on **(c)** the head and **(d)** buttocks. **(e)** Skin biopsy from the hyperkeratotic plaque on the buttock showed parakeratotic scale, regular elongation of the rete ridges, dilated capillaries, and lymphocyte-dominant infiltrate in the upper dermis (Scale bar shows 100 μm).

3. Discussion

Compared with European and American AD phenotype, Asian AD phenotype is characterized by changes in the psoriasiform phenotype: increased epidermal hyperplasia, more frequent parakeratosis, and focal hypogranulosis, associating with higher Th17 activation(3). A skin biopsy before dupilumab initiation in our case also showed psoriasiform dermatitis with IgE and TARC elevation, which is typical of Asian AD phenotype.

Psoriasis and AD are suggested to be on a polar Th17-to-Th2 spectrum and show distinct phenotypes responding to different cytokines. Psoriasis is associated with the overproduction of IL-17, and AD is associated with that of IL-4 and IL-13(4). A recent study demonstrated that IL-4 abrogates Th17-mediated inflammation(5). Thus, the blockade of IL-4/IL13 signaling by dupilumab may induce Th17-dominant inflammation in the skin, resulting in psoriasis eruption.

To the best of our knowledge, this is the first report of psoriasis onset in Asian AD patient treated with dupilumab. It is possible that Asian patients show psoriasiform phenotypes more frequently after treatment with dupilumab, but further study is needed to confirm this hypothesis.

Conflict of interest disclosure

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Trends in Immunotherapy

Focus and Scope

Trends in Immunotherapy (TI) is an open access, peer-reviewed journal encompassing various disciplines related to all immune-based areas. TI has a target audience consisting of scientific researchers, professional practitioners and medical scholars from academia, medical industry, and education, etc. It provides a forum to share scholarly practice to advance the immunotherapy in the combination of science and medicine.

TI publishes original research articles, review articles, editorials, mini-review articles, case reports, commentaries, correspondence articles, database articles, perspective articles, short reports, etc. Preliminary studies, pre-clinical and clinical investigative reports are welcomed.

The research topics of TI include but are not limited to:

1. Cancer immunotherapy
2. Targeted therapy and tumor microenvironment
3. Immune dysregulation, skin barrier dysfunction
4. Chemoimmunotherapy
5. Antibodies
6. Immunomodulators, inhibitors and intensifiers
7. Therapeutic method for auto-immune disorder
8. Efficacy of drug immunotherapy
9. Allergy disorder and immunotherapy
10. Immunotherapy cell-products
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