Department of Dermatology

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General Summary

We have organized special clinics for selected skin diseases, including viral diseases, neurofibromatosis type 1, atopic dermatitis, psoriasis, contact dermatitis, and skin cancers. Integrating concentrated clinical efforts and related basic research should provide a significant contribution to excellent clinical practice.

Research Activities

Psoriasis

Various systemic therapies, including oral cyclosporin microemulsion preconcentrate, methotrexate, etretinate, topical vitamin D3, and corticosteroids, have been used, depending on disease severity and the degree to which quality of life (QOL) is impaired in individual patients. Also phototherapy, including psoralen ultraviolet A, narrow-band ultraviolet B (UVB), and the 308-nm exicimer lamp, are effective and have been administered in a newly organized skin-care clinic. We have evaluated patients' QOL reflecting social background and have developed a Japanese version of the Psoriasis Disability Index. We also developed a Japanese version of the Work Productivity and Activity Impairment questionnaire for psoriasis. We examined the incidence of metabolic syndromes as a comorbidity of psoriasis. In a special psoriasis clinic, we select patient-based treatments to satisfy patients' demands. New biologic agents, including infliximab, adalimumab, and ustekinumab, are available and have been used to treat intractable psoriasis. Clinical trials have been performed with new biologic agents, including antibodies against interleukin (IL) 17A, IL-23p19, and janus kinase 1/3 inhibitor.

Atopic dermatitis

The pathogenesis of atopic dermatitis has been attributed to a complex interaction of the environment, host susceptibility genes, altered skin barrier function, and the immune system. Recently, psychosocial factors have been suggested to influence the exacerbation of atopic dermatitis. Therefore, we are treating patients on the basis of both evidence-based medicine and QOL issues. We try to obtain a precise medical history from each patient and to learn how QOL is impaired. To support this type of approach, we have organized skin-care lessons in the Skin-Care Clinic twice a week and have hosted an atopic dermatitis forum, which includes monthly lectures and group meetings. For basic clinical research, the levels of substance P, thymus and activation-regulated cytokine, and IL-31 related to pruritus in atopic dermatitis are being evaluated according to disease

severity. Clinical trials of opioid-κ-receptor have been performed.

Malignant skin tumors

We have been studying clinical courses, postoperative outcomes, and genomic and expression changes in patients with malignant melanoma, extramammary Paget's disease, squamous cell carcinoma, basal cell carcinoma, malignant peripheral nerve sheath tumor, malignant fibrous tumors, and cutaneous T-cell lymphomas. For the accurate diagnosis of pigmented tumors, we always perform dermoscopic examinations and sentinel lymph-node biopsy, especially for patients with stage II or III melanoma. We are participating in collaborative clinical research for maintenance therapy using local injections of interferon β and in several nationwide epidemiological studies.

Neurofibromatosis

Because the number of registered patients in our clinic is the largest in Japan and because many patients with letters of introduction visit from all over Japan, we concentrate on long-term follow-up and improvement of impaired QOL by means of accurate diagnosis and the resection of neurofibromas. The estimated lifetime risk of malignant peripheral nerve sheath tumor (MPNST) in patients with neurofibromatosis 1 is 10%, although information concerning the epigenetic abnormality is limited. We have used the methylation-specific polymerase chain reaction (PCR) and real-time reverse transcriptase (RT)-PCR to analyze the methylation status of tumor suppressor genes and cancer-testis genes in established MPNST cell lines. The findings of abnormal expression of several cancer-testis genes and the inactivation of tumor suppressor genes indicate that disarranged methylation and demethylation are involved in the ontogenesis of MPNST.

Herpes virus infection

1. Herpes simplex virus

We treat patients with genital herpes and intractable oral/facial herpes. Rapid diagnostic procedures by means of immunohistochemical staining with monoclonal antibodies against herpes simplex virus (HSV)-1, HSV-2, and varicella-zoster virus (VZV) are performed in this clinic. We also perform enzyme-linked immunosorbent assays of antibodies against HSV glycoproteins G-1 and G-2 for patients with genital herpes to determine the type of HSV. After the diagnosis is confirmed, suppressive therapies (patient-initiated therapy and episodic therapy) with varaciclovir are started to improve the impaired QOL.

2. Herpes zoster and postherpetic neuralgia

Initial treatments for herpes zoster and postherpetic neuralgia (PHN) are performed in this clinic. Neurological complications are commonly associated with herpes zoster. PHN, defined as pain present for 90 days after the onset of rash, is a major sequela of VZV infection and impairs QOL. To prevent PHN, we proactively use tricyclic antidepressants. Posthoc analyses of a subgroup of patients showed that amitriptyline in combination with acyclovir reduced the incidence of PHN. PHN is characterized by various types of pain and sensory symptoms, including ongoing pain, allodynia, and evoked or spontaneous intermittent lancinating pains. We prescribe pregabalin, tricyclic antide-

pressants, selective serotonin reuptake inhibitors, opioid analgesics, such as Tramcet® (Grunethal Ltd., Stokenchurch, UK), which contains tramadol hydrochloride and acetominophen. Tramadol is a weak μ-opioid receptor agonist that induces serotonin release and inhibits the reuptake of noradrenaline. We use visual analogue scales and an objective measuring device (Pain Vision PS-2100, Nipro Co., Osaka) to evaluate the effect of treatment.

Human papillomavirus infection
In addition to ordinary cryotherapy, topical vitamin D3 and salicylic acid have been used to treat viral warts. Contact immunotherapy using squaric acid dibutylester, CO_2 laser, pulsed dye laser, and glutaraldehyde have also been used to treat severe, intractable viral warts. Human papillomavirus infection typing with the PCR has regularly been performed for bowenoid papulosis and rare viral warts. Five percent imiquimod cream is now available for the treatment of condyloma acuminatum.

Contact dermatitis/drug eruption
We have performed patch testing to identify causes of contact dermatitis and drug eruption.

Laser
The Q-switched ruby laser is useful for treating nevus Ota, acquired dermal melanocytosis, and ectopic Mongolian spot because of its selective photothermolysis. Such treatment is covered by health insurance. Senile freckles are usually successfully treated with a single treatment, but treatment is not covered by health insurance, so is performed at the patient's personal expense. On the other hand, nevus spilus is difficult to treat with the Q-switched ruby laser because it often recurs after 1 to 2 months. The efficacy of a pulsed dye laser for treating hemangiomas and telangiectasia depends on the clinical type, location, patient age, and other factors. The pulsed dye laser was effective for treating hemangioma simplex on the face or neck of young adults. The size and redness of the strawberry mark can be reduced if treatment is started before the age of 6 months. The recently introduced V-beam laser is effective for intractable vascular lesions. We have been able to use the V-beam laser since 2011. Because the ultrapulse CO_2 laser has higher energy and a shorter pulse width, it can vaporize at a fixed depth and can be used to quickly remove actinic keratosis, seborrheic keratosis, syringoma, and epidermal nevus.

Skin Care Clinic
Narrow-band UVB irradiation is performed for patients with psoriasis, atopic dermatitis, prurigo nodularis, vitiligo, or cutaneous T-cell lymphomas. Targeted phototherapy equipment, such as the 308-nm excimer lamp, is also used. Other special clinics, including those for skin care lessons, therapeutic make-up, acne care, mental care, and *kampo* medicine, are available to patients on demand.

Self-assessment

Psoriasis: To improve patients' QOL and treatment compliance, we have selected therapies on the basis of their risk/benefit ratios. Phototherapy with narrow-band UVB and the 308-nm excimer lamp has been introduced. New biologic agents, including infliximab, adalimumab and ustekinumab, have been also used to treat patients with severe psoriasis.

Neurofibromatosis: Many patients with neurofibromatosis type I are still being referred to our special clinic. We are now performing inheritance consultation for pediatric patients. Surgical removal of different types of neurofibroma is performed for inpatients and outpatients to enhance QOL. Genetic analysis was performed for MPNST.

Herpes virus infection: Suppressive therapy has been used to improve impaired QOL. Surveys of QOL in patients with recurrent genital herpes and drug sensitivities derived from HSV are also being performed. To control PHN, we are prescribing tricyclic antidepressants, serotonin reuptake inhibitors, Tramcet® and other opioid analgesics, and topical analgesics.

Human papillomavirus infections: We have employed new treatments, including topical vitamin D3, contact immunotherapy, and laser, in addition to ordinary surgical treatments, to treat refractory viral warts. Human papillomavirus typing is also regularly performed.

Contact dermatitis: Causal chemicals, environmental allergens, drugs, and foods in patients with contact dermatitis, are regularly performed patch testing.

Atopic dermatitis: We have been treating patients according to established guidelines and the degree of QOL impairment. The psychosocial background of patients is also considered. To increase patient understanding, we have been organizing atopic dermatitis forums, which include monthly lectures and group meetings. Basic research is focused on pruritogens, such as substance P, IL-31, Th2 chemokines, and thymus and activation-regulated cytokine.

Malignant skin tumors: We have been treating many patients with skin cancers, including melanomas, basal/squamous cell carcinoma, and extramammary Paget's disease, with surgical operations combined with sentinel lymph-node biopsies and chemotherapy. At the same time, we have provided supportive care to improve QOL for patients with incurable conditions.

Laser: We have been treating many patients using several different types of laser. In the stubborn cases of hemangioma simplex, strawberry mark, and teleangiectasia, we have been able to use the V-beam laser since 2011.

Collagen vascular diseases: Intimate and periodic follow-up is performed in cooperation with other departments.

On the basis of many clinical and basic results, it is possible to select appropriate treatments for diverse aspects of skin diseases in our department.

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