



FIGURE 1: The mass on the left buttock was $20 \times 10 \times 4$ cm in diameter and its surface was cauliflower-shaped with profuse exudates and ulceration. The skin around the mass colored brownish to purplish and had ulcers likely penetrating to the mass.

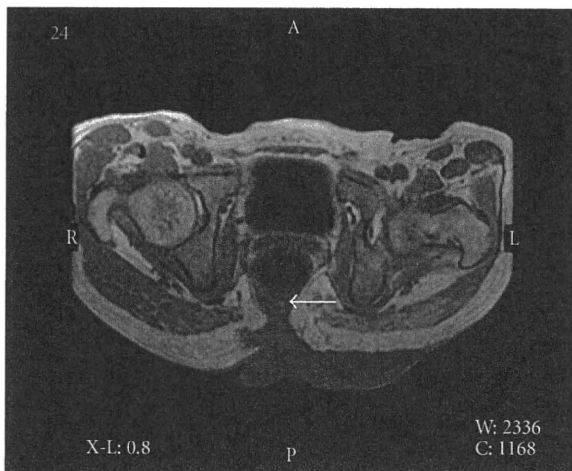


FIGURE 2: The mass invaded into coccygeal bone and the rear side of rectum (arrow).

penetrating to the mass. The patient noticed a part of an elongated oval nodule in childhood and its rapid growth in his late thirties. He stated that the nodule had grown to huge.

Computed tomography (CT) and magnetic resonance imaging (MRI) (Figure 2) showed that the mass invaded into coccygeal bone and the posterior wall of the rectum. While bilateral inguinal lymph nodes were slightly swollen, no apparent visceral metastasis was detected.

Histologically, under low magnification, the tumor cells grew upward with keratinization and downward intermingling hypertrophic scar. Under high magnification, the tumor included papilliform-acanthosis, a number of cancer pearls and individual cell keratinization (Figure 3). Atypical

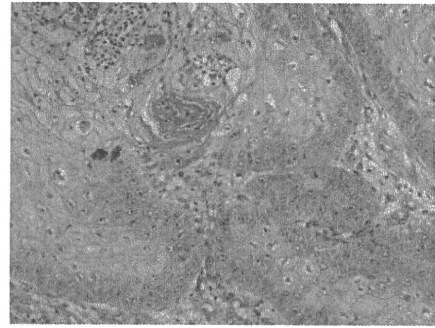


FIGURE 3: Histologically, the tumor includes papilliform-acanthosis, a number of cancer pearls, and individual cell keratinization.

epidermis contained numerous mitoses and moderate to severe cell atypia. Two of bilateral inguinal lymph nodes were also biopsied as sentinel lymph nodes, and no histopathological metastasis was detected. These findings led the diagnosis of well-differentiated squamous cell carcinoma (SCC) T4N0M0 according to AJCC staging.

We selected initial treatments with combination of cisplatin, fluorouracil (5-FU), and pepleomycin and concurrent 50 gray of irradiation because the tumor margin was not as demarcated as an ensured excision. As a consequence of the treatments, the tumor became necrotic and crumbled, and finally, it markedly shrank to a 7×3.5 cm ulcer. After chemoradiation therapy, a washy red smooth nodule was noticed from the beneath of tumor. It was adjeent to the ulceration (Figure 4). The ulcer was considered to be located at the site where the SCC originated from. The patient stated that it was the nodule that he noticed in childhood and a part of which became huge.

Since there is no evidence of metastasis during the above treatments, we decided to perform a radical operative procedure to achieve complete control of the tumor. According to the first extent of tumor, it was excised together with sacrococcyx and rectum. The perineum was reconstructed with a pedicled musculocutaneous flap using the right abdominal rectus muscle, and sigmoid colostoma was created (Figures 5 and 6).

Macroscopically, the division surface of tumor showed a white fibrous tissue. Surprisingly, histopathological findings showed no remaining tissue of SCC but showed only fibrous. The fibrosis reached to rectum, and tissues was also seen around the trabecula of the sacrococcyx, suggesting previous invasion of the tumor. The nodule located behind the huge SCC showed papilliform structure which invaginated to the dermis and the wall was consisted with two layers of epithelial cells. The outer layer of the epithelium was composed of cuboidal cells and the inner layer of columnar cells. Many plasma cells infiltrated to the interstitial area (Figures 7(a) and 7(b)). According to these findings the nodule was diagnosed as SP.

Three courses of chemotherapy with the same regimen as a neoadjuvant one were performed after surgery. Fifteen months after the operation, the patient is well and working without any local recurrence and metastasis.



FIGURE 4: A washy red smooth nodule was noticed from the beneath of tumor after chemoradiation therapy. It was adjacent to the ulceration.

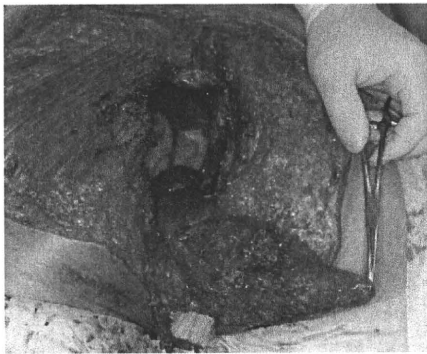


FIGURE 5: According to the first extent of tumor, buttock skin was excised together with sacrococcyx, and rectum. Reconstructive surgery by musculocutaneous flap of abdominal rectus muscle and colostomy was performed.

3. Discussion

In the present case, we paid attention to the following two points. One is tumor origin, especially the relationship between long-existed SP and SCC. The other is tumor's intensive expansion and effectiveness of our treatments.

Because buttock is not sun exposed site and our patient was relatively young among the patients who have SCC, to elucidate the origin of SCC in the present case is important. The patient and his family argued that upper part of a nodule in his buttock, which he noticed from his childhood, grew larger and became the large tumor.

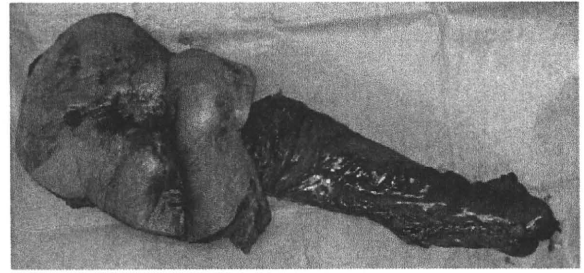


FIGURE 6: The excised specimen. The buttock skin, sacrococcyx and rectum were excised together.

Indeed, the nodule appeared from the beneath of tumor after chemoradiation therapy. It was histologically diagnosed as SP. At first, we suspected that the origin of his SCC was not SP but chronic pyoderma because of the purplish pigmentation of his buttock and deep invasion [7]. However, he denied the symptom of pyoderma before development of SCC. Moreover, the purplish color was observed only in the skin lying directly on the tumor and right buttock skin was normal. Therefore, we believe that chronic pyoderma seems not to precede SCC. Cases of SP existing as a single tumor together with nevus sebaceous have been reported. And SP and nevus sebaceous are considered to share the same origin from the primary epithelial-germ. Apocrine differentiation of the germ cells leads SP, though not as well-differentiated as in sebaceous nevus [8]. And sebaceous nevus is known as an origin of many kinds of benign and malignant neoplasms including SCC [9]. Thus, the SCC in the present case may arise from sebaceous nevus existed together with SP. However, in our patient, no histopathologic features of sebaceous nevus were found. There are a few reports of SCC [4] and verrucous carcinoma [5, 6] arising from SP. Cases of syringocystadenocarcinoma papilliferum which showed histological findings of SCC are also reported [10, 11]. As a result, it is conceivable that SCC in the present case originated from SP itself, germ cells of which can differentiate to keratinocytes, although we could not determine the continuity of the SP and SCC histologically, because SCC had disappeared at the time of operation.

As for the second point, the tumor extended to the depth of rectum. To our knowledge, there was no report of SCC case treated by such a very extensive resection together with rectum and coccyx. Unexpectedly, despite this massive local invasion, no metastasis and local recurrence have been observed for long. It may suggest that chemoradiation therapy and extensive operation we performed was effective treatment for such a huge SCC. No microscopic existence of tumor cells in lymph and blood vessels may lead to a favorable clinical course.

In conclusion, we report a rare case of massive SCC of the buttock infiltrating deeply to the rectum, which was treated by extended radical operation and obtained long-term survival without local recurrence or metastasis. It was suspected that the tumor developed from SP which had existed from childhood.

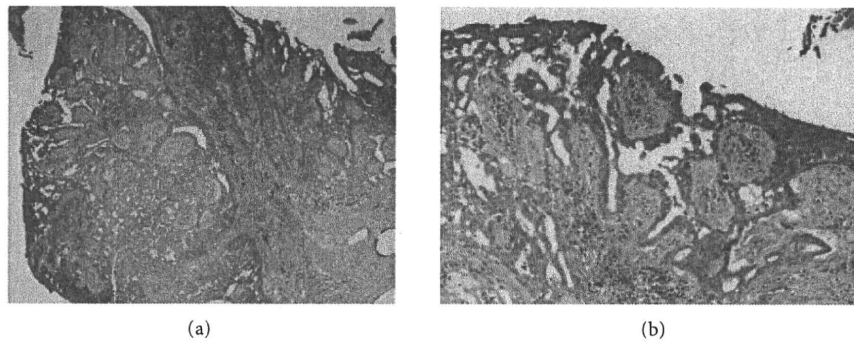


FIGURE 7: The nodule appeared after chemoradiation therapy showed papilliform structure with invagination to the dermis and the wall was consisted with two layers of epithelial cells. The outer layer of the epithelium was composed of cuboidal cells and the inner layer of columnar cells. Many plasma cells infiltrated to the interstitial area.

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LETTER TO THE EDITOR

Superimposed linear psoriasis

Dear Editor,

An 18-year-old Chinese man presented with multiple pruritic erythematous patches and plaques over his trunk and extremities. His family reported that he began developing linear erythematous scaly plaques over his left upper extremity at 3 years of age. Thereafter, at 17 years of age, he developed multiple pruritic erythematous scaly papules, patches and plaques on the trunk and extremities. At the same time, the preceding linear erythematous plaques became prominent over his left upper extremity, accompanied by severe pruritus. His family history was negative for psoriasis.

A physical examination demonstrated linear band-like scaly erythematous papules and plaques along Blaschko's lines, extending from the dorsum of the left hand over the left forearm and elbow to the left arm with excoriation (Fig. 1). In addition, there were multiple erythematous macules, papules and plaques on the trunk, buttocks and lower extremities (Fig. 2).

Two biopsy specimens were obtained from the left arm in the linear band-like plaque and erythematous small plaque on the back. The biopsy specimen obtained from the left arm showed parakeratosis with Munro's microabscesses, elongated rete ridges, mild lymphocytic infiltration in the upper dermis and dilated vessels in the dermal papillae, consistent with psoriasis vulgaris (Fig. 3). The second biopsy specimen demonstrated similar findings. An immunohistochemical study was performed on the specimen obtained from the linear lesion on the left arm. Involucrin was expressed prematurely in most of the supra-basal keratinocytes. This finding was also consistent with psoriasis.¹

The patient was prescribed calcipotriol/clobetasol propionate two-compound ointment. Most of the psoriatic lesions almost completely resolved with postinflammatory hyperpigmentation. However, the linear band-like lesion on the left upper extremity



Figure 1. Linear band-like scaly erythematous plaques extending from the dorsum of the left hand over the forearm with excoriation.

improved only slightly, showing resistance to this therapy.

Linear psoriasis is a rare variant of psoriasis. Characteristic aspects of linear psoriasis include erythematous-squamous lesions along Blaschko's lines, an absence of pruritus and onset at an early age. In our case, non-linear common psoriatic plaques developed 14 years later. Recently, the term "superimposed linear psoriasis" was proposed as a descriptive term for such cases.²

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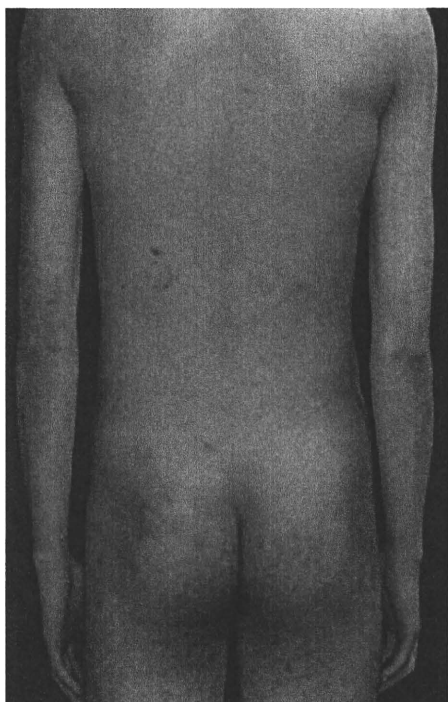


Figure 2. Multiple non-linear erythematous macules and plaques on the trunk and buttocks.

The linear lesions resemble inflammatory linear verrucous epidermal nevus (ILVEN). Characteristic clinical aspects of ILVEN are unilateral linear verrucous or psoriasiform lesions along Blaschko's lines. Altman and Mehregan described the diagnostic criteria: (i) early age onset; (ii) predominance in women; (iii) frequent involvement of the left lower extremity; (iv) pruritus; (v) persistence of lesions; and (vi) refractory to treatment.³ Criteria (ii) and (iii) are now considered to have limited diagnostic value.

The differentiation between linear psoriasis and ILVEN is usually very difficult. Therefore, the differential diagnosis has been disputed in the published work over recent decades.⁴⁻⁷ ILVEN differs histopathologically from linear psoriasis by areas of hypergranulosis with orthohyperkeratosis alternating with areas of agranulosis with parakeratosis. Involucrin expression is absent in the parakeratotic epidermis of ILVEN, whereas involucrin is expressed in the suprabasal epidermis in linear psoriasis.¹ In our case, the histological findings including involucrin expression all favored linear psoriasis.

Psoriasis is considered to be one of the inflammatory diseases with a polygenic background. A subject

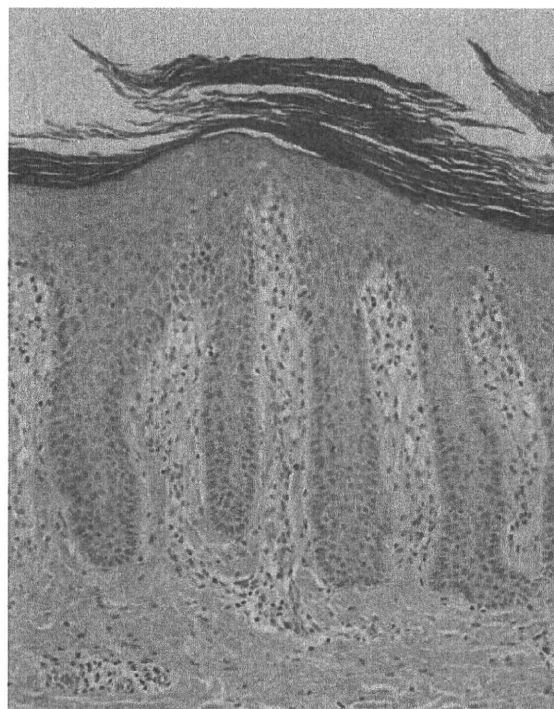


Figure 3. Histological features of the linear band-like lesions on the left arm. These findings are consistent with psoriasis vulgaris (hematoxylin-eosin, original magnification $\times 50$).

having several genes that predispose toward psoriasis would develop the disease when environmental factors trigger it.

Linear psoriasis may be explained by the following "type 2 mosaicism" concept.^{2,8} A patient has heterozygosity in one of the genes that predispose to psoriasis. Crossing over of the gene would occur in a somatic cell during the early development of skin, resulting in a loss of heterozygosity (LOH), which gives rise to daughter cells that are homozygous or hemizygous for the gene. These daughter cells distribute along Blaschko's lines and are more susceptible to psoriasis. This concept would offer an explanation as to why the linear lesions preceded the non-segmental lesions and showed resistance to topical therapy.⁹

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A Case of Juvenile Dermatomyositis Manifesting Inflammatory Epidermal Nevus-Like Skin Lesions: Unrecognized Cutaneous Manifestation of Blaschkitis?

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ABSTRACT

Background: Juvenile dermatomyositis is potentially life threatening rare autoimmune illness that mainly affects muscle and skin. Cutaneous features are useful in establishing the diagnosis of this disease.

Case Summary: We report an 8-year-old male juvenile dermatomyositis who presented epidermal nevus like-lesions on the back of the right thigh. Characteristic cutaneous changes such as Gottron's papules of the hand, heliotrope rash of the eyelids, and poikiloderma-like lesions on the back were observed. Diagnosis of juvenile dermatomyositis was made by positive muscle biopsy and magnetic resonance imaging findings and typical cutaneous manifestations. However, epidermal nevus-like skin lesions, an acquired inflammatory dermatosis that follows Blaschko lines, seen in this case have been rarely reported in the literatures.

Discussion: We would like to report this case and discuss about the significance and pathogenesis of this rare cutaneous manifestation like Blaschkitis in juvenile dermatomyositis.

KEY WORDS

blaschkitis, epidermal nevus like-lesions, Gottron's papules, heliotrope, juvenile dermatomyositis, poikiloderma

ABBREVIATIONS

JDM, juvenile dermatomyositis; ANA, anti-nuclear antibody; AD, atopic dermatitis; MRI, magnetic resonance imaging.

INTRODUCTION

Dermatomyositis is a multi-system autoimmune disorder primarily affecting the skin and skeletal muscle. Among dermatomyositis, juvenile dermatomyositis (JDM) occurs about 10 cases per year in Japan and manifests characteristic clinical features such as dystrophic calcinosis of the skin, elevated serum IgE or rare association with interstitial pneumonitis or malignancy in addition to typical skin manifestations seen in adult patient with dermatomyositis.^{1,2} Therefore, it is important to recognize, diagnose and medi-

cate JDM in early stage of the disease. Generally the typical skin rash proceeds before the onset of muscle weakness. However, rare skin manifestations such as inflammatory epidermal nevus-like lesion as documented in the present communication occasionally result in some confusion at the daily practice. Therefore, dermatologist should be careful to recognize the variety of skin manifestations seen in the patients with JDM.

CASE REPORT

The patient is an 8-year old male who had no remark-

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Fig. 1 Gottron's papules. Note small erythematous or violaceous, flat papules and small plaques on the dorsa of the knuckles and finger joints.



Fig. 3 Epidermal nevus-like-erythema on the back of the right thigh.

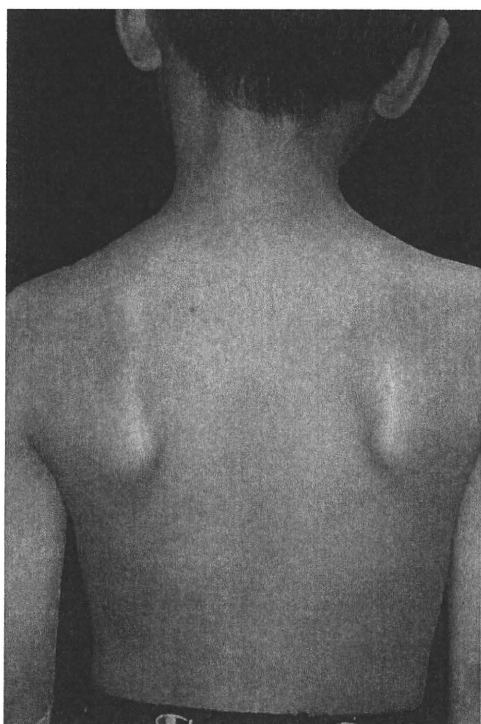


Fig. 2 Poikiloderma-like lesions on the back.

able past history and family history. He had had slightly keratinized and itchy skin rash on the anterior side of the lower legs since October 2005, and noticed easy fatigability when he first consulted the dermatological clinic at June 2006. Topical steroid and oral antihistamine treatment failed to improve his complaints. Adversely violaceous papules developed on the each knuckles, extensor surface of elbows, and knees. A liquid nitrogen treatment was enforced them resulting in unfavorable clinical response. Skin rashes extended gradually on the face, extremities and trunk thereafter. Topical vitamin D3 under the diagnosis of pityriasis rubra pilaris, did not show any favorable effect. The patient was consulted to us at October 19, 2006 for further clinical evaluation and additional therapy.

On physical examination, several cutaneous changes were demonstrated as follows. (I) a purplish heliotrope erythema of the eyelids, (II) Gottron's papules: small erythematous or violaceous, flat papules and small plaques on the dorsa of the knuckles and finger joints (Fig. 1), (III) many scratch marks on the diffuse spreading erythema on the chest and abdomen, (IV) poikiloderma-like lesions with distinct border and scratch marks on the back (Fig. 2), and (V) erythema with white silver scale on the extensor surface of elbows, and knees, keratinized and violaceous papules with zosteriform-distribution on the back of the right thigh mimicking

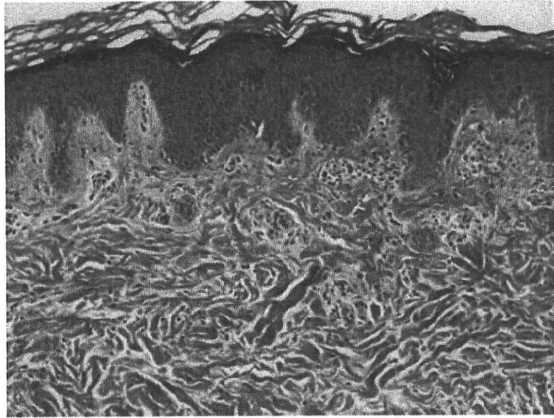


Fig. 4 Skin biopsy specimen from the erythema on the right hand (H-E stain, magnification: $\times 40$). Histological examination of skin biopsy specimen from the right hand showed hyperkeratosis without parakeratosis, liquefaction degeneration and lymphocytic infiltration surrounding vessels.

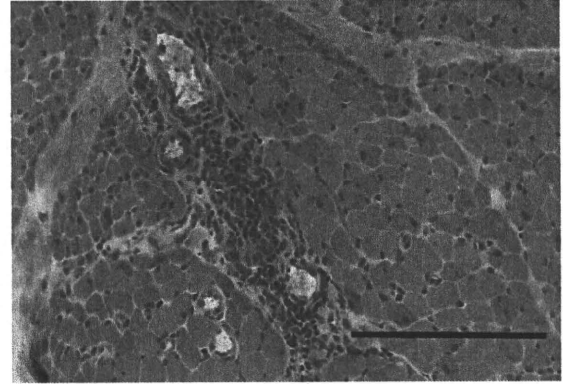


Fig. 5 Muscle biopsy specimen from the right biceps brachii (H-E stain, Scale Bar: 0.2 mm). Muscle biopsy specimen from the right biceps brachii muscle showed infiltration by inflammatory cells surrounding blood vessels and atrophy of muscle fiber.

epidermal nevus (Fig. 3). Hematological examination showed following abnormal data: WBC $4.28 \times 10^3/\mu\text{l}$ (eosinophil 16.3%), aldolase 9 U/l, anti-nuclear antibody (ANA) $\times 160$ (ANA pattern HO+SP), IgE-RIST 2500 IU/ml, IgE-RAST (house dust 100<). Serum anti-Jo-1 antibody was negative. Histological examination of skin biopsy specimen from the right hand showed hyperkeratosis without parakeratosis, liquefaction degeneration and lymphocytic infiltration surrounding vessels (Fig. 4). Alcian blue-stain showed deposition of mucin in dermis (data not shown). Unfortunately, because of an absence of parental consent, a skin biopsy of the inflammatory epidermal nevus-like skin lesion was not performed.

In this case, the patient had chronic eczema, peripheral blood eosinophilia and high serum IgE level. Based on these findings, differential diagnosis of atopic dermatitis (AD) might be considered. However skin rash are not typical for AD and histological findings are consistent with dermatomyositis rather than those of AD. Finally, we diagnosed him as JDM. Muscle biopsy specimen from the right biceps brachii muscle showed infiltration by inflammatory cells surrounding blood vessels and atrophy of muscle fiber (Fig. 5). A T2-weighted magnetic resonance imaging (MRI) scan showed high-intensity lesion symmetrically in each quadriceps femoris muscles. Gower's sign, dysphagia and dysarthria were not observed, but tonus of proximal muscles was diminished. A chest roentgenogram did not suggest interstitial pneumonitis signs.

We have administrated oral prednisolone 0.5 mg/kg/day and methotrexate 15 mg/m²/week and used topical steroid for skin rash since November 15, 2006. Currently, skin rash including verruciformis papules on the posterior site of the right thigh almost disap-

peared. Weakness of the muscle strength also improved, and serum aldolase level returned normal level.

DISCUSSION

In this case, the violaceous rash on the posterior of right thigh was clearly different from other typical rash seen in JDM. The rash seems to distribute along Blaschko line and looked like epidermal nevus or blaschkitis.³ It was noteworthy that this skin lesion began to appear with other characteristic rash of JDM and clearly disappeared after systemic therapy for JDM. From this characteristic clinical course, we consider that the epidermal nevus-like lesion seen in this case is a variant of flagellate erythema. There are some reports of the flagellate erythema mainly as a side effect of bleomycin. A few cases appeared it in patients with DM without bleomycin therapy. The manifestation of flagellate erythema was described as linear violaceous streak, pruriginous lesion and zebra-like stripe eruption.^{4,5} However, a skin biopsy of the lesion was not taken because the patient and his mother disagree to take the skin biopsy, we can never deny the diagnosis of epidermal nevus. Histopathology of flagellate erythema in DM is non-specific.^{4,6} Physical injury, minor trauma and sun exposure have been speculated as causative agents of flagellate erythema.³ In this case, flagellate erythema might be induced by scratching. Interestingly, we found a report that DM patients with flagellate erythema were positive for anti-155/140 kDa nuclear proteins antibody more frequently than DM patients without flagellate erythema.⁷ Internal malignancy was found more frequently in anti-155/140-positive DM patients than anti-155/140-negative DM patients while prevalence of interstitial pneumonia in anti-155/140-positive DM patients was lower than anti-155/140-negative DM patients.⁷ However, the antibody

prevalence in JDM patients under 13 years old has not been reported. Because these complications might determine the prognosis of DM, it seems to be favorable that anti-155/140 should be measured if the JDM patients have flagellate erythema. It is advocated that flagellate erythema-associated DM may be more frequent than reported in the literature. Identically, flagellate erythema-associated JDM may be more frequent than reported. The analysis of the relationship between flagellate erythema and anti-155/140 is very interesting and additional study is expected in the future.

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The Japanese version of this work, which did not undergo peer review, was published as the report in the *Practical Dermatology*.⁸ The article title of this English version has been modified because this is more informative for the readers. This English version does not alter the data or interpretations of the Japanese version.

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Impact of Sedative and Non-Sedative Antihistamines on the Impaired Productivity and Quality of Life in Patients with Pruritic Skin Diseases

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ABSTRACT

Background: The impairment that pruritic skin diseases have on patient productivity at work, in the classroom, and in daily activities is substantial and needs to be characterized. The objective of this study was to determine how pruritic skin diseases impact patient productivity and quality of life (QOL), in order to improve the measurement of these endpoints to allow the influence of treatment options including sedative and non-sedative antihistamines to be analyzed.

Methods: The impact of pruritic skin diseases and the effect of antihistamine therapy on work, classroom, and daily productivity were evaluated using the Work Productivity Assessment Index-Allergy Specific Questionnaire. The intensity of itch and patient QOL were assessed using a visual analogue scale and Skindex-16, respectively.

Results: Pruritic skin diseases resulted in significant impairment of work, classroom, and daily productivity. The severity of overall work impairment in atopic dermatitis (AD), urticaria, and prurigo was higher than for other diseases analyzed. However, classroom activity was more adversely affected in patients with urticaria relative to other diseases. All pruritic diseases in this study negatively impacted daily activity to a similar degree. Impaired productivity was significantly improved in patients taking non-sedative antihistamines for 1 month, and the improvements correlated with the alleviation of itch and improved QOL.

Conclusions: These results indicate that pruritic skin diseases reduce patient productivity at work, in the classroom, and during daily activities, and that non-sedative antihistamines may offer an advantage over sedative antihistamines for alleviating certain negative consequences of these skin diseases.

KEY WORDS

antihistamine, productivity, pruritic, quality-of-life, skin diseases, WPAI-AS

INTRODUCTION

The impaired quality of life (QOL) and diminished work and classroom productivity of individuals with pruritic skin diseases is a matter of public concern.^{1,2} Furthermore, estimates of the impact of pruritic skin diseases on the economic loss in businesses and school performance records have attracted a great deal of interest worldwide.^{3,4} Similar unfavorable impacts were identified for certain skin diseases, such

as chronic idiopathic urticaria, psoriasis, and chronic hand dermatitis.⁵⁻⁸ The Work Productivity Assessment Index (WPAI) is commonly used to determine the impact of health and disease on certain parameters related to patient productivity. According to the WPAI, the estimated percent of overall work impairment due to psoriasis, urticaria, and chronic hand dermatitis is 15%, 25%, and 29%, respectively.^{5,6,8}

Itching is a key characteristic of allergic skin diseases that dramatically affects a patient's quality of

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life.^{9,10} Thus, it is possible that itching alone would affect patient performance in the work place. The allergy specific WPAI (WPAI-AS) can be used to more effectively assess productivity in these patients as itching is a common symptom of allergy-related skin diseases. Recently, we reported the effect of antihistamines on productivity of patients with pruritic skin diseases using the WPAI-AS assessment questionnaire.^{11,12} On average, pruritic skin diseases impaired overall workplace productivity, classroom productivity, and daily activity by 39%, 45%, and 42% at baseline, respectively.¹² Furthermore, non-sedative antihistamines (mainly fexofenadine) reduced the intensity of itch and improved work productivity. In contrast, sedative antihistamines failed to improve work productivity, but significantly decreased itch intensity.¹² However, the relative impact of different pruritic diseases on work productivity has not been assessed. In this report, the WPAI-AS evaluation system was applied to each subgroup of patients with different diagnoses of pruritic skin diseases, and the degree of impairment for each disease at baseline was compared using a linear least-squares method. Furthermore, itch severity and patient QOL were assessed using a visual analogue scale (VAS) and Skindex-16, respectively. Finally, after validating the relationships between these parameters, we propose a method to approach the treatment of pruritic skin disease that will improve overall productivity in the workplace, in the classroom, and in daily activities.

METHODS

PATIENTS AND STUDY DESIGN

This study was conducted between April, 2008 and March, 2009. After obtaining approval from the Institutional Review Board (IRB), patients with pruritic skin diseases ($n = 216$) from Osaka University Hospital or its affiliated hospitals, gave informed consent to participate in this study. The final number of valid responses was $n = 206$ (male : female=93 : 113; mean age \pm SD: 52 ± 20 years). Patients with skin diseases associated with underlying systemic diseases (e.g., serious liver disease, renal dysfunction, and blood diseases), history of epilepsy, history of a previous drug allergy, or women who were pregnant or lactating were excluded from this study. Participants received no medical attention during the week before study initiation. The selection of therapy for each patient, such as oral antihistamines versus external medicine (e.g., steroid ointments, tacrolimus ointments, or certain moisturizers), was left to the physician's discretion (open-label trial). Fexofenadine ($n = 72$) and loratadine ($n = 2$), anti-histamines for which the package insert contained no cautionary statement regarding sedative actions, were categorized as "non-sedative". All other antihistamines were classified as "sedative".

STUDY INSTRUMENTS

The Skindex-16 quality-of-life instrument¹³ was used to measure the effect of pruritic skin diseases on QOL. The magnitude of the itch sensation was assessed using a VAS (0-100, "0" indicates no-symptom, and "100" indicates most severe symptom). Work and classroom productivity were assessed with the WPAI-AS instrument (score range, 0-100%; higher percentages indicate higher productivity).¹¹ Work productivity, classroom productivity, and daily activity impairment (%I) were calculated by the effects of the pruritic skin diseases on productivity while working/attending class or other daily activities during the past 7 days. The percentage of work/classroom time missed (%TM = TM/TW) was calculated by the number of work/classroom hours missed due to allergy (TM) and the usual number of hours worked/attending class (TW). Finally, the percentage overall impairment was calculated as follows: $\%TM + ([100 - \%TM] \times I\%) = \% \text{ overall impairment}$.¹¹ These instruments were patient-administered before (baseline) and 1 month after treatment initiation.

STATISTICAL ANALYSIS

The one-sample *t*-test was used for analysis of differences between two groups. Pearson's product-moment correlation coefficient was used to determine the significance of correlations between two parameters (Table 1, 2). To examine the significance of the contingency between the certain categorical data, Fisher's exact test (for evaluating the significance between the two kinds of classifications) and Cochran-Mantel-Haenszel general association statistics (for evaluating more than 3 kinds of classifications) were performed (Table 3). The bias of evaluative consequences to one variable was analyzed using univariate analysis (Table 4). A linear least-squares method was used to evaluate the degree of impairment in each disease at baseline. Because heterogeneity of starting values was inevitable, the effect measures illustrated in Figure 1 were evaluated using linear models. The results and confidence intervals for the improvement variations were compared visually for each parameter using a forest plot. Improvement variations (change ratios) were calculated as follows: $\text{change ratio} = (\text{evaluated value 1 month after the initiation of treatment-baseline value}) / (\text{baseline value})$. In all tests, values of $P < 0.05$ were considered statistically significant.

RESULTS

STUDY POPULATION CHARACTERISTICS

A total of 216 patients with pruritic skin disease entered the study, and data from 206 patients (average age of 52 ± 20 years) who completed the study were used for analysis. Company employees and part-time workers represented 48% of the patients ($n = 99$), and retired seniors and unemployed individuals ac-

Table 1 Correlations between baseline parameters and patient outcomes

	Correlations to baseline patient parameters [P-value, Pearson's coefficient of correlation (r), n]		
	Itch VAS	Skindex-16 score	Activity impairment
Allergic pruritic skin diseases (AD and urticaria)			
Overall work productivity impairment	NS (r = 0.2443, n = 52)	P < 0.001 (r = 0.5674, n = 51)	P < 0.001 (r = 0.6712, n = 52)
Overall classroom productivity impairment	NS (r = 0.1948, n = 14)	NS (r = 0.0915, n = 13)	NS (r = 0.1833, n = 14)
Activity impairment	P = 0.006 (r = 0.2893, n = 89)	P < 0.001 (r = 0.7051, n = 84)	-
Non-allergic skin diseases (All other excluding AD and urticaria)			
Overall work productivity impairment	NS (r = 0.2904, n = 44)	P < 0.001 (r = 0.4813, n = 46)	P < 0.001 (r = 0.8584, n = 47)
Overall classroom productivity impairment	NS (r = 0.2604, n = 4)	NS (r = 0.7963, n = 4)	P = 0.0014 (r = 0.9986, n = 4)
Activity impairment	P < 0.001 (r = 0.3332, n = 107)	P < 0.001 (r = 0.5170, n = 109)	-

NS, not statistically significant; vs., versus.

Table 2 Correlative relationships between antihistamine treatment groups and the improvement ratio of itch VAS scores to Skindex-16, overall work productivity impairment, and activity impairment

	Correlations to baseline patient improvement ratios by treatment group [P-value, Pearson's coefficient of correlation (r), n]	
	Non-sedative AH	Sedative AH
Skindex-16 score vs. itch VAS	P < 0.001 (r = 0.5769, n = 69)	NS (r = 0.2360, n = 99)
Overall work productivity impairment vs. itch VAS	P = 0.0042 (r = 0.4539, n = 38)	NS (r = 0.2462, n = 46)
Activity impairment vs. itch VAS	P = 0.0046 (r = 0.3448, n = 66)	NS (r = 0.1203, n = 92)

NS, not statistically significant; AH, anti-histamines; VAS, visual analogue scale.

counted for 43% (n = 89). Students made up a relatively small fraction of the study group (n = 18, 9%). Patients diagnosed with eczema/dermatitis had the highest representation (36%) among participants, followed in decreasing order by patients with urticaria, atopic dermatitis (AD), pruritus, prurigo, and psoriasis (Table 5).

ASSESSMENT OF WORK, CLASSROOM, AND ACTIVITY IMPAIRMENT

Table 6 shows the baseline work, classroom, and daily activity WPAI-AS productivity scores. Due to the relatively small sample size of each disease group, statistically significant differences in impairment between disease groups were not detected (Fig. 2). However, the results indicate that the overall impairment of work, classroom, and daily activity productivity tended to be larger in the atopic dermatitis, eczema/dermatitis, and urticaria disease groups (Fig. 2). There were also some interesting group-specific observations. Prurigo showed higher overall impairment of work productivity and daily activity. Individuals with urticaria had relatively higher percentages of

impairment of overall classroom productivity than that observed in other skin diseases. Daily activity was impaired at high percentages for individuals with AD.

CORRELATION BETWEEN PRODUCTIVITY IMPAIRMENT AND SKINDEX-16, OR LOSS OF DAILY LIFE PRODUCTIVITY

To check the validity of the assessment procedures in this study, we looked for correlations between impaired productivity at work, in the classroom, and in daily activities. In addition, correlations between overall activity impairment, the magnitude of itch sensation as assessed by VAS, and QOL measures as assessed by Skindex-16 were analyzed (Table 1). As shown in Table 1, correlation analyses were divided between allergic (atopic dermatitis and urticaria) and non-allergic skin diseases (all other diagnosis groups). Results specific for allergic skin diseases indicated that impairment in overall work productivity showed a positive correlation with the itch VAS, Skindex-16, and the impairment in daily activity. A correlation between impairment in overall classroom

Table 3 Distribution of patient characteristics in the sedative and non-sedative antihistamine treatment groups

Background factors	Non-sedative AH		Sedative AH		P-value [†]	
	n	%	n	%		
Age	<50	42	56.8	55	45.8	0.183
	≥50	32	43.2	65	54.2	
Gender	Male	37	50.0	48	40.0	0.183
	Female	37	50.0	72	60.0	
Disease	AD	20	27.0	22	18.3	0.515
	Ec/der	26	35.1	45	37.5	
	Urticaria	16	21.6	33	27.5	
	Other	12	16.2	20	16.7	
Occupation	Worker	45	60.8	51	42.5	0.017
	Student	8	10.8	10	8.3	
	Other	21	28.4	59	49.2	
Duration of disease	<5 years	46	62.2	74	61.7	1.000
	≥5 years	21	28.4	34	28.3	

[†]Differences in the distribution of patients between sedative and non-sedative antihistamine groups was determined by the Fisher's exact test for age, gender, and duration of disease and by the Cochran-Mantel-Haenszel general association statistic for disease diagnostic group and occupation. AH, antihistamines; AD, atopic dermatitis; Ec/der, eczema/dermatitis.

Table 4 Impact of background factors on the improvement of WPAI-AS score

Patient characteristics	Impact of patient characteristics on overall productivity impairment (P-value)		
	Overall work impairment	Overall classroom impairment	Daily activity impairment
Age	0.345	0.2986	0.3556
Gender	0.4454	0.5464	0.2615
Disease	0.0646	0.5349	0.4118
Duration of disease: <5 years, ≥5 years	0.0053	0.4793	0.2528
Occupation: worker, student, other	N/A	N/A	0.5097

N/A, not applicable.

productivity and itch VAS, Skindex-16 score, and activity impairment was not observed for the allergic skin diseases (Table 1). However, in the allergic skin disease subgroup there was a positive correlation between the impairment in daily activity and the magnitude of itch and Skindex-16 scores.

Similar analyses were performed on the subgroup of patients with all other skin disease diagnoses except atopic dermatitis and urticaria. This group was designated the non-allergic skin disease group even though varying causative conditions including allergic and non-allergic mechanisms could be responsible for symptoms related to eczema/dermatitis. As shown in Table 1, the correlation profile of this subgroup was very similar to that of the allergic skin disease subgroup with one major difference. There was a significant correlation between overall classroom productivity and activity impairment in the non-allergic skin disease subgroup (Table 1).

IMPACT OF ANTIHISTAMINES ON PATIENT OUTCOMES

Patients were treated with non-sedative antihistamines ($n = 74$), sedative antihistamines ($n = 121$), or

external medication ($n = 11$) for a duration of 1 month (Table 7). The patient characteristics in the physician-assigned treatment groups of sedative and non-sedative antihistamines were all well-matched with the exception of occupation (Table 3). We previously reported that the impaired productivity in pruritic skin diseases was significantly improved in patients taking non-sedative antihistamines.¹² Interestingly, for patients taking non-sedative antihistamines in this study, the improvement ratio as assessed using the VAS score showed a significant correlation with improvements in the Skindex-16 score, the reduction in overall work productivity impairment, and the reduction in daily activity impairment. No significant correlations were found among patients taking sedative antihistamines (Table 2).

To eliminate the bias for starting value dispersion, the effects of non-sedative and sedative antihistamines on overall work productivity, daily activity, and overall classroom productivity were corrected by grouping according to background factors or baseline value using the linear least-squares methods (Fig. 1A). Results indicated that non-sedative antihistamines produced greater overall improvements in pro-

Novel Outcomes in Pruritic Skin Disease

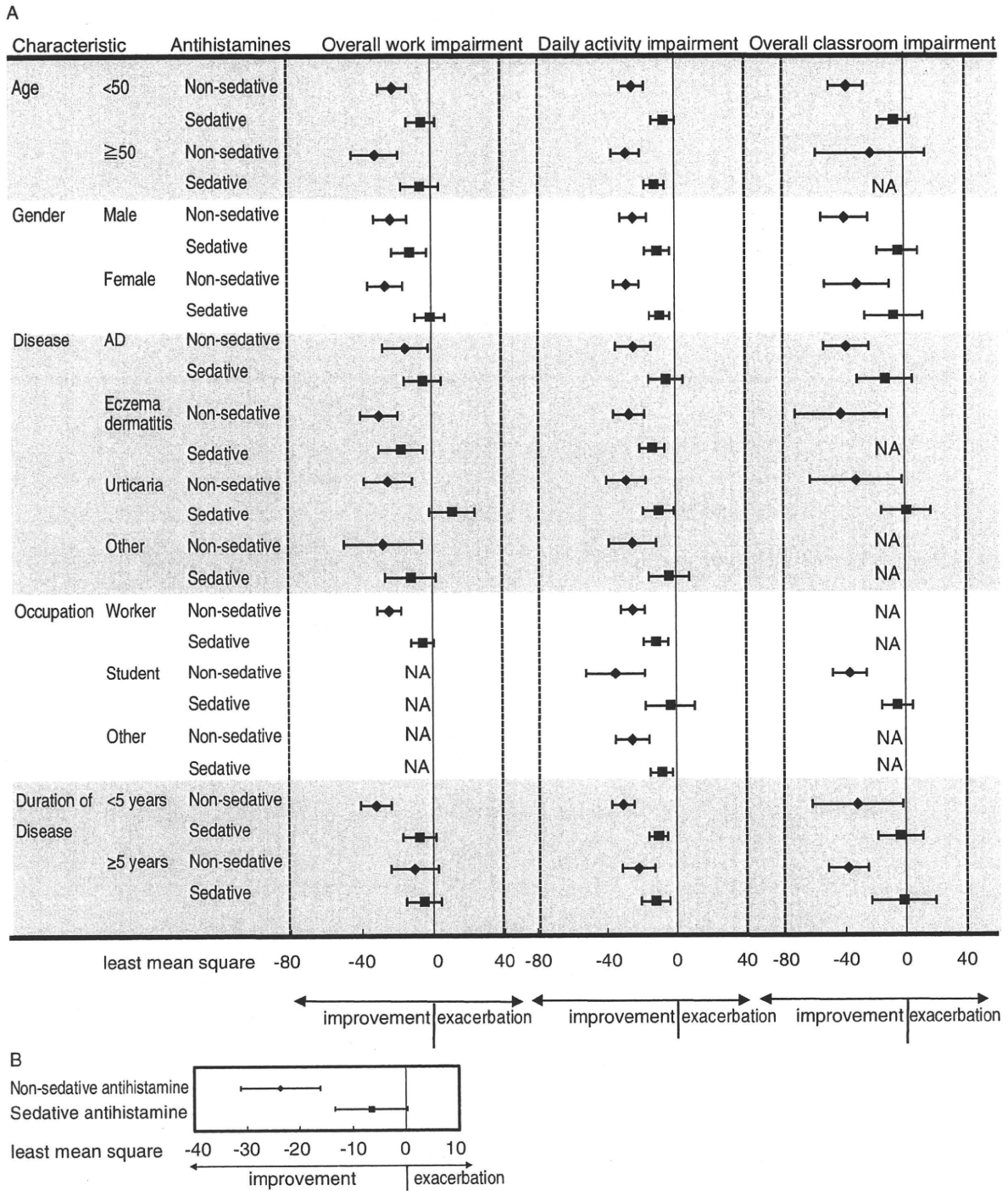


Fig. 1 **A.** The impact of antihistamines on overall work productivity impairment, activity productivity impairment, and overall classroom productivity impairment per-certain parameters of pruritic skin diseases. Changes in the evaluated value of certain parameters from baseline were adjusted with background factors and the initial value (a linear model). Results are shown in a forest plot. Horizontal lines indicate 95% confidence intervals. The rhomboid or square dot on center of the horizontal line indicates the point estimate. Significance is indicated by horizontal lines that do not overlap with the vertical line of least mean square = 0. NA, not applicable. **B.** Comparison of overall work impairment (amount of change) adjusted by background factor (disease duration).

Table 5 Characteristics of patient population by pruritic skin disease diagnostic group

Disease	(n)	Male	Female	Average age (yrs ± SD)	Average duration of disease (yrs ± SD)
Atopic dermatitis	43	21	22	33.7 ± 10.1	17.1 ± 13.2
Eczema/dermatitis	75	33	42	61.9 ± 17.8	3.1 ± 8.1
Urticaria	50	17	33	47.3 ± 16.3	5.4 ± 10.1
Pruritus	14	9	5	64.3 ± 18.1	3.4 ± 3.6
Prurigo	8	6	2	59.8 ± 16.6	2.1 ± 1.5
Psoriasis	7	4	3	49.3 ± 19.6	1.1 ± 1.4
Others [†]	9	3	6	54.7 ± 18.2	10.8 ± 14.9

[†] Includes patients with systemic lupus erythematoses, tinea pedis, toxicoderma, polymorphic light eruption, von Recklinghausen disease, tuberous sclerosis, scabies, bullous pemphigoid, and lupus erythematoses.

Table 6 Baseline WPAI-AS productivity scores (Mean ± SD)

	AD	Ec/Der	Urticaria	Pruritus	Prurigo	Psoriasis	Others
Work	(n = 31)	(n = 31)	(n = 21)	(n = 2)	(n = 5)	(n = 3)	(n = 6)
Work productivity impairment	38.7 ± 26.3	41.0 ± 24.8	33.8 ± 25.8	20.0 ± 0	36.0 ± 18.2	26.7 ± 25.2	23.3 ± 29.4
Work time missed	4.9 ± 11.4	2.6 ± 10.3	10.6 ± 26.8	0	12.2 ± 21.7	2.2 ± 3.8	0
Overall work productivity impairment	40.4 ± 26.8	41.3 ± 25.2	41.8 ± 29.5	20.0 ± 0	42.9 ± 24.8	28.9 ± 21.7	23.3 ± 29.4
Classroom	(n = 8)	(n = 1)	(n = 6)	(n = 1)	(n = 0)	(n = 1)	(n = 1)
Classroom productivity impairment	41.3 ± 25.3	50.0	63.3 ± 15.1	0	-	0	10
Classroom time missed	0	0	14.5 ± 17.8	0	-	0	0
Overall classroom productivity	41.3 ± 25.3	50.0	70.1 ± 10.5	0	-	0	10
Activity	(n = 43)	(n = 72)	(n = 46)	(n = 14)	(n = 8)	(n = 7)	(n = 9)
Activity impairment	50.2 ± 26.9	41.8 ± 23.0	37.6 ± 26.4	37.9 ± 20.1	46.3 ± 22.0	44.3 ± 28.8	34.4 ± 29.2

AD, atopic dermatitis; Ec/Der, Eczema/Dermatitis; SD, Standard deviation.

ductivity in patients with skin diseases than sedative antihistamines (Fig. 1A). Non-sedative antihistamines significantly improved work productivity under almost all background conditions with the exception of disease duration. Sedative antihistamines only had a significant impact on the subpopulation of patients that were male or those that had a diagnosis of eczema/dermatitis (Fig. 1A).

The duration of disease was the only baseline patient characteristic that could significantly influence or bias the outcomes seen from administration of antihistamines (Table 4). Therefore, we compared the amount of change in the overall work impairment in the sedative and non-sedative antihistamine treatment groups after adjusting for the baseline duration of disease (Fig. 1B). These results confirmed that non-sedative antihistamines significantly improved the overall work impairment, while sedative antihistamines did not (Fig. 1B). Evaluation of impact of antihistamines on daily activity impairment and overall classroom impairment also demonstrate the superiority of non-sedative antihistamines over sedative antihistamines (Fig. 1A). Interestingly, sedative antihistamines failed to improve overall classroom productivity in all the patient population groups analyzed (Fig. 1A).

THE EFFECT OF ANTIHISTAMINES ON ATOPIC DERMATITIS

The effect of antihistamines on atopic dermatitis is still controversial.^{14,15} Therefore, the treatment effects specifically for patients with atopic dermatitis ($n = 43$) were analyzed independently from other diagnostic groups (Fig. 3). As expected, treatment with antihistamines significantly reduced itch intensity in atopic dermatitis, while external medicines were ineffective (Fig. 3A). No differences were found between patients taking non-sedative versus sedative antihistamines (Fig. 3A). The impact of all treatments on the Skindex-16 QOL measure was similar to that for the itch VAS, with a significant effect for all antihistamines, but not for topical medications (Fig. 3B). Both non-sedative, and sedative antihistamines improved overall work impairment without statistical significance (Fig. 3C). Alternatively, the non-sedative antihistamine significantly reduced activity productivity impairment, whereas the trend towards improvement seen with sedative antihistamines did not reach statistical significance (Fig. 3D). These patients were prescribed concomitant external medications, but there were no remarkable differences between the non-sedative and sedative antihistamines treatment groups (Fig. 3E).

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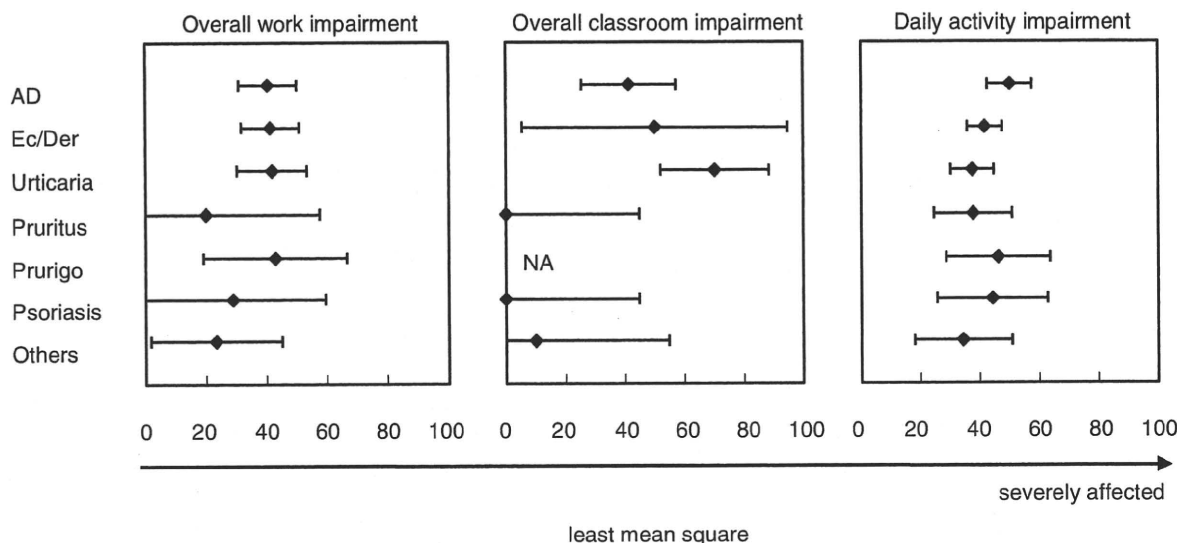


Fig. 2 Forest plots demonstrating the degree of impairment in each disease at baseline was evaluated using a linear least-squares method. Horizontal lines represent 95% confidence intervals. The rhomboid dot on the center of horizontal line indicates the point estimate. NA, not applicable.

Table 7 Number of patients from each skin disease diagnostic group assigned to indicated treatments

	Sedation	n	AD	Ec/Der	Urticaria	Pruritus	Prurigo	Psoriasis	Others
Fexofenadine	NS	72	20	26	14	5	1	1	5
Loratadine	NS	2	0	0	2	0	0	0	0
Olopatadine	S	53	8	18	18	2	3	3	1
Epinastine	S	8	3	3	0	0	0	2	0
Cetirizine	S	9	2	6	0	0	1	0	0
Ebastine	S	11	1	7	1	1	0	0	1
Other 2 nd generation	S	19	5	5	7	1	0	0	1
1 st generation	S	21	3	6	7	2	2	1	0
External medicine	-	11	1	4	1	3	1	0	1
Total	-	206	43	75	50	14	8	7	9

AH, anti-histamines; NS, non-sedative; S, sedative; AD, atopic dermatitis; Ec/Der, Eczema/Dermatitis.

DISCUSSION

This study demonstrates that allergic skin diseases may have detrimental effects on productivity at work, in the classroom, and during daily activity. Previous reports demonstrated that allergic rhinitis impaired mean overall productivity at work, in the classroom, and in daily activity by ratios of 27-48%, 33-47%, and 42-51%, respectively.¹⁶⁻¹⁹ In the present study, work performance and daily activities were highly and similarly impaired in patients with allergic skin diseases. However, WPAI-AS baseline scores in our study were slightly high relative to previous reports of WPAI (unidentified version) baseline scores for chronic idiopathic urticaria, psoriasis, and chronic hand dermatitis.^{5,6,8} It is not currently clear why the present study generated different WPAI baseline scores, but further investigation is warranted.

According to the WPAI-AS values for the various pruritic skin diseases, the impairments in classroom productivity and overall classroom productivity were higher for patients with urticaria (Fig. 2). To clarify the reason why urticaria affected classroom productivity, cases of students with urticaria were analyzed independently for correlations with certain parameters (data not shown). Only the Skindex-16 was significantly associated with classroom impairment in this group ($P = 0.0075$, $r = 0.9282$, $n = 6$). Presumably, urticaria may impair a student's classroom productivity by negatively impacting their QOL.

In previous reports, WPAI scores of overall work impairment in patients with psoriasis were lower than those for patients with chronic idiopathic urticaria and chronic hand dermatitis.^{5,6,8} Pearce and colleagues⁶ discussed the observation that QOL measures did not exhibit the same trend as WPAI score in

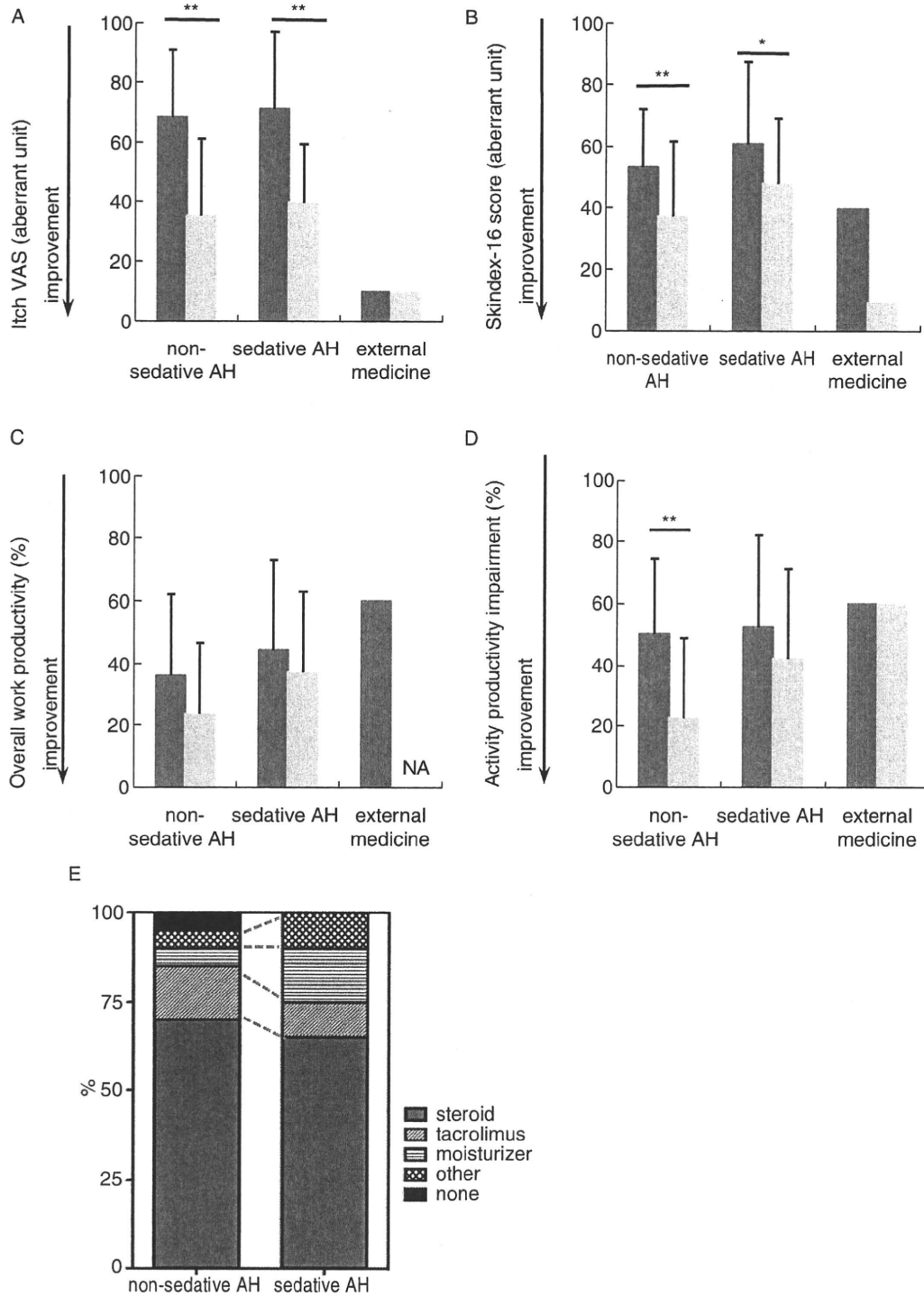


Fig. 3 The impact of antihistamines on (A) itch VAS, (B) skindex-16 score, (C) overall work productivity impairment, and (D) daily activity productivity impairment in atopic dermatitis. The data of baseline assessment (dark gray bar) and post treatment assessment (light gray bar) are shown as mean ± SD. **Statistically significant improvement compared with the data of baseline assessment ($P < 0.001$), * $P < 0.01$. NA, not applicable; AH, antihistamines. (E) Concomitant external medicine for cases with atopic dermatitis. "Other" includes vitamin D3 or non-steroidal anti-inflammatory ointment.

patients with psoriasis, and indicated that estimating the impact of psoriasis on social life seemed to be difficult. Indeed, as the number of patients with psoriasis was low in this study, which may indicate that our data are not representative of the general population of patients with psoriasis.

Concerning WPAI-AS scores in patients with atopic dermatitis, the total loss of daily activities was relatively higher than for patients with other skin diseases (Table 6, Fig. 2). It has been said that the intensity of itch might be increased in a relaxed environment, such as coming home or at nighttime.²⁰ In support of this, daily activity in patients with atopic dermatitis or pruritus was severely impaired compared with the impairment in overall work productivity (Table 6). Thus, daily activity may be highly susceptible to impairment in patients with atopic dermatitis and pruritus.

The differences between patients taking non-sedative versus sedative antihistamines was also addressed. As previously reported, sedative antihistamines failed to reduce work productivity impairment despite decreasing itch VAS values and Skindex-16 measures.¹² Impaired performance as an adverse effect of sedative antihistamines may be a major factor in these divergent results. In fact, in patients treated with sedative antihistamines, the improvement ratio for itch VAS scores did not significantly correlate with either the Skindex-16 QOL measure, the reduced impairment in overall work productivity, or the reduced impairment in daily activity (Table 2). Additionally, the extent of impairment in overall work productivity can be predicted by the Skindex-16 measures (Table 1). Nevertheless, clinicians should keep in mind that they could overestimate the effect of sedative antihistamines to improve on work productivity by relying solely on patient itch-intensity and QOL values. For these reasons, non-sedative antihistamines have substantial value in the treatment of patients with pruritic skin diseases.

However, the criteria for selecting antihistamines differ from disease to disease and vary worldwide. It is well known that non-sedative antihistamines, but not sedative antihistamines, are recommended as first-line agents for urticaria treatment.²¹⁻²⁵ In contrast, many previous published reviews, guidelines, and position papers on the care of atopic dermatitis state that the antihistamines are no more than a supportive management for pruritus, and their sedative properties offer an advantage for reducing the magnitude of itch in atopic dermatitis.^{14,15,26,27} Thus, there is a tendency worldwide to recommend sedative antihistamines for the treatment of atopic dermatitis with intense itch or sleep disturbance.^{14,15,26} Our data challenge this trend, since non-sedative antihistamines reduced the impairments in daily activity in patients with atopic dermatitis, while sedative antihistamines were ineffective (Fig. 1A, 3). Accordingly, the criteria

for selecting antihistamines in certain skin diseases should be reconsidered.

Limitations of this study include the number of patients in each group and the potential influences of the adverse global economic conditions. Nonetheless, this report may highlight a new goal in the treatment of pruritic skin diseases and provide a rationale for shifting the choice of treatment options to non-sedative antihistamines.

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