Clinical Case Report

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Mycosis fungoides patient accompanied actinic keratosis, actinic keratosis with squamous cell carcinoma transformation, and porokeratosis after NBUVB therapy – 1st case report and review of the literature

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Abstract

Introduction: Mycosis fungoides (MF) is the most common form of primary cutaneous T cell lymphoma. Narrowband ultraviolet B light (NBUVB) is used increasingly in treating MF because of its good toleration and well-established management.

Concerns: To discuss the risk factors and underlying pathogenic factors in the patients with secondary skin diseases after NBUVB therapy.

Methods: We report in details the first case of a patient with MF accompanied with actinic keratosis (AK), AK with squamous cell carcinoma (SCC) transformation and porokeratosis after NBUVB therapy. Meanwhile, Sequence variants in tumor suppressor p53 gene in the patient's specimens were detected. A literature search of the key word "narrowband ultraviolet B light "and "side effects" was performed on PubMed, 14 cases of this entity were found. A total of 15 patients including our case were reviewed in this study and meaningful conclusion could be drawn.

Outcomes: The mean age at diagnosis of secondary skin dermatoses after NBUVB therapy was 62.08 years with a male to female ratio of 2:1. The cases were reported more in Europeans than in Asians (2.75:1), and the Fitzpatrick skin type was mainly Ito III (12/15). The mean cumulative number and cumulative dose of UVB treatments were 43.71 and 42, 400 (mJ/cm^2), respectively. There was a positive relationship between Fitzpatrick skin type and cumulative dose of UVB treatments. Among the secondary skin diseases after NBUVB treatment, 12 were tumors, 2 were non-tumorous dermatoses. Only our patient presented with both. By polymerase chain reaction-single nucleotide polymorphism (PCR-SNP) analysis, C–G mutation of exon 4 of p53 was found in AK and MF specimens in our patient.

Conclusion: To our knowledge, our case is the first MF patient accompanied with AK, AK with SCC transformation and Porokeratosis after NBUVB treatment. Lower Fitzpatrick skin type may be the risk factor of secondary skin diseases after NBUVB treatment.

Abbreviations: AK = actinic keratosis, BCC = basal cell carcinoma, IFN-α = interferon-α, MF = mycosis fungoides, NBUVB = narrowband ultraviolet B light, PCR-SNP = polymerase chain reaction-single nucleotide polymorphism, SCC = squamous cell carcinoma.

Keywords: actinic keratosis, mycosis fungoides, NBUVB, porokeratosis, squamous cell carcinoma

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1. Introduction

Mycosis fungoides (MF) is the most common form of primary cutaneous T cell lymphoma, its treatment is always the focus of attention. Traditionally, classic MF undergoes 3 stages: the patch, plaque, and tumor stages. According to the disease stage, prognostic factors, patient age, and the impact on quality of life, MF has different therapies, including skin-directed, systemic, targeted therapies, and chemotherapy. Skin-directed therapies, such as topical corticosteroids, topical nitrogen mustard (mechlorethamine hydrochloride), topical retinoids, and phototherapy, are the 1st-line treatments for early stage of MF (stages IA–IIA).[1] As 1 type of phototherapies, narrowband ultraviolet B light (NBUVB) is increasingly used in MF because of its good toleration, well-established management, and lower photocarcinogenicity. However, some side effects have been reported in MF patients treated with NBUVB in the literature. Herein, we report the 1st case of a patient with a long-standing history of MF, who accompanied with actinic keratoses (AKs), AK with squamous cell carcinoma (SCC) transformation, and porokeratosis, and review the cases with secondary skin diseases after NBUVB therapy.

2. Methods

2.1. Case report

The clinical data of a patient diagnosed with MF combined with AK, AK with SCC transformation, and porokeratosis were retrieved from the files in Dermatology Department, Union Hospital, Tongji Medical Collage, Huazhong University of Science and Technology, P.R. China. The histopathological slides were re-examined by 2 senior dermatopathologists, and the diagnosis was made on the basis of clinical and pathological features of MF, AK, AK with SCC transformed, and porokeratosis.

2.2. Consent

This study adhered to the tenets of the Declaration of Helsinki. Informed consent was signed by the patient for the publication of this report and its related images.

2.3. Polymerase chain reaction-single nucleotide polymorphism (PCR-SNP) analysis

The paraffin embedded specimens of AK and MF were subjected to PCR-SNP analysis where total DNA extraction was extracted using TIANquick FFPE DNA Kit (TIANGEN BIOTECH, Beijing, China) according to the Manufacturer's protocol. Using specific upstream and downstream primers, exons 4–9 of the p53 gene were amplified separately encompassing intron–exon junctions. Human p53 gene was searched in the National Center for Biotechnology Information (NCBI). All primers were designed by Primer Premier 3.0. Two microliters of the lysates were used as templates in a 30 μL solution containing 10× buffer; 2.5 mM each of deoxyadenosine triphosphate, deoxyguanosine triphosphate, deoxycytidine triphosphate, and deoxythymidine triphosphate; upstream and downstream primers (10p each); and 5 U Ex Taq DNA polymerase (TAKARA BIO INC, Tokyo, Japan). PCR was carried out in a PTC-200 PCR cycler (BIO-RAD) as follows: the DNA was denatured at 96 °C for 5 minutes followed by 1 cycle at 96 °C (20 seconds), 55 °C (30 seconds), and 72 °C (30 seconds); 35 cycles at 96 °C (20 seconds), 72 °C for 5 minutes to complete the extension. All PCR products were purified using PCR Purification plate (Millipore, Darmstadt, Germany) and subsequently sequenced using BigDyeTerminator V. 3.1 Cycle Sequencing Kit and ABI 3730XL Genetic Analyzer (both Applied Biosystems, Darmstadt, Germany). The PCR program was as follows: 95 °C for 15 minutes, followed by 35 cycles of 95 °C for 15 seconds, 50 °C for 5 seconds, and 60 °C for 90 seconds. In addition, human hematal DNA included in every PCR reaction was a normal control.

2.4. Literature review

PubMed was searched with the keyword "narrowband ultraviolet B light" and "side effects" on May 20, 2016 to identify and assess all-related cases and their relevant citations. We obtained the following data: age, sex, country, skin type, treatment, cumulative number of UVB treatments, cumulative dose of UVB treatments, and secondary skin disease type. The relationship between the factors was analyzed.

3. Results

3.1. Case report

A 54-year-old woman with skin type III had a 27-year history of erythematous, scaly, pruritic lesions that appeared initially on her limbs, and later spread to involve her trunk. Generalized plaque-type mycosis fungoides (MF) was diagnosed in 2001, stage IIA (T2 N1 B0 M0). Before NBUVB therapy, she had taken interferon-α (IFN-α) intramuscularly every other day at a dosage of 100 to 300 million units intermittent treatment for almost 10 years. In 2012, she was taken 3 times NBUVB treatment (starting from 500 mJ/cm^2) combined with IFN-α 300 million units intramuscularly every other day for a week with good clinical response initially. But she could not tolerate the widespread redness of the skin and itchiness and gave up the treatment. Later on, the erythematous, scaly lesions spread to her lower limbs. From 2013 to 2015, the patient took the above regimens again, and a total number of NBUVB treatments were 105 (cumulative dose of 72,850 mJ/cm^2), but the MF lesions were not completely under control.

On March 1st, 2016, the patient came to visit a local Dermatology clinic for a flesh-colored nodule and plaques on her left inguinal region. The nodule and one of the plaques were excised. The nodule was diagnosed as SCC. The plaque lesion was given a description with no specific diagnosis. To make the definite diagnosis and seeking further treatment, the patient came to visit our Dermatology Department on March 19, 2016. Physical examination showed that there were multiple sporadically distributed 2 to 10 cm in diameter, erythematous scaly and hyperkeratotic plaques on her left thigh, lower abdomen, and right leg (Fig. 1A, D). By reviewing the previously excised nodular specimen from the inner thigh, it showed the features of AK with SCC transformation. In both sides of the nodular lesion, hyperkeratosis, parakeratosis, and acanthosis of the epidermis and atypical cells with enlarged, irregular, hyperchromatic nuclei were found in the lower part of the epidermis and basal cells (Fig. 2A–C). The above changes are the features of AK. In the center of the lesion, the epidermis down grew into the dermis, and there were different sized squamous nests with nuclear pleomorphism, mitoses, and prominent keratinization (Fig. 2A, D). The plaque lesion from the very vicinity of the nodule showed both the features of AK and porokeratosis. The later showed a thin column of parakeratotic cells (cornoid lamella) with an absent underlying granular layer and dyskeratotic cells in the spinous zone (Fig. 2E,

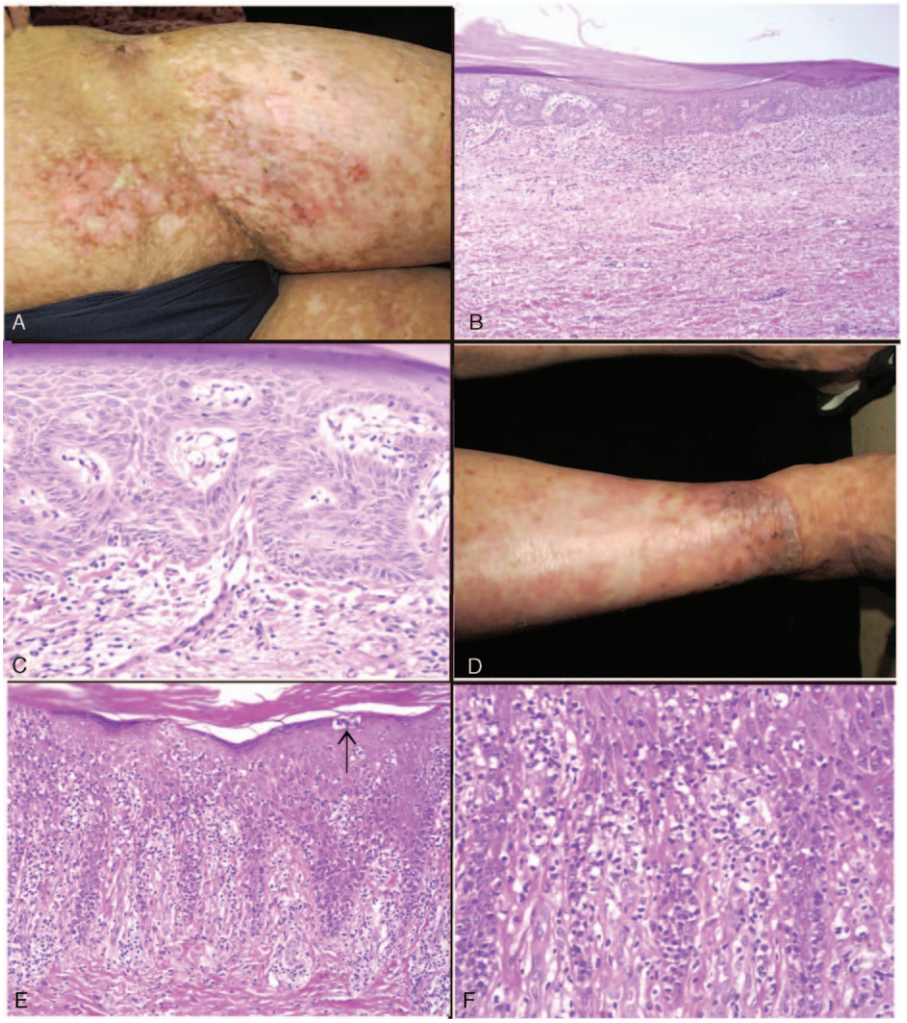

Figure 1. (A) Multiple erythematous plaques with hyperkeratosis on the left inguinal area. (B) There is parakeratosis overlying a thickened epidermis with florid keratosis (hematoxylin and eosin 100×). (C) Basal cell atypia with enlarged, irregular, hyperchromatic nuclei is present (hematoxylin and eosin 400×). (D) The erythematous scaling plaques on the right leg. (E) The epidermis shows psoriasiform hyperplasia with Pautrier microabscess (arrowed), epidermotrophism, hyperchromatic lymphocytes infiltrating (hematoxylin and eosin 200×). (F) High power shows atypical irregular lymphocytes with well developed halo (hematoxylin and eosin 400×).

F). Ten large sized, clinically diagnosed AK lesions were surgically removed in our hospital and all of which showed similar features of AK (Fig. 1B, C). One lesion from the right leg showed Pautrier microabscess, epidermotrophism, and hyperchromatic lymphocytic infiltrate in the dermis (Fig. 1E, F). A diagnosis of MF accompanied with AK, AK with SCC transformation, and porokeratosis induced by NBUVB was established. The small-sized lesions were treated with cryotherapy. The MF lesions were treated with nitrogen mustard. The patient was told to keep regular follow-up.

3.2. PCR-SNP analysis of the specimens from our patient

C–G mutation of exon 4 of p53 gene was found in the lesions of AK and MF specimens of our patient, but no mutations in other exons were found (Fig. 3).

3.3. Clinical findings

The PubMed search yielded 14 cases of skin diseases after NBUVB treatment. Totally, 15 cases were documented and analyzed in this study including our case (Tables 1 and 2). The mean age at diagnosis was 62.08 years (51.07–88.7 years old). There were 10 males (66.67%) and 5 females (33.33%). The male:female ratio was 2:1. The cases were reported more in Europeans (11 cases) than in Asians (4 cases) with a ratio of 2.75:1. Fitzpatrick skin type was mainly I to III (12/80%). The others were not specified (3/20%). The mean cumulative number and cumulative dose of UVB treatments were 43.71 (6–146) and 42,400 (319–239,000) mJ/cm^2, respectively. A positive relationship between Fitzpatrick skin type and cumulative dose of UVB treatments was noticed (Fig. 4). Among the secondary skin diseases after NBUVB treatment, 12 were tumors (80%) and 2 were nontumorous diseases (13.33%). Only our patient presented with both.

4. Discussion

NBUVB has been used for the treatment of MF since 1999.[1] It has been reported that the patients who have received long-term psoralen and ultraviolet A treatment had an increased risk of developing skin cancer.[7] Similar results have been observed in

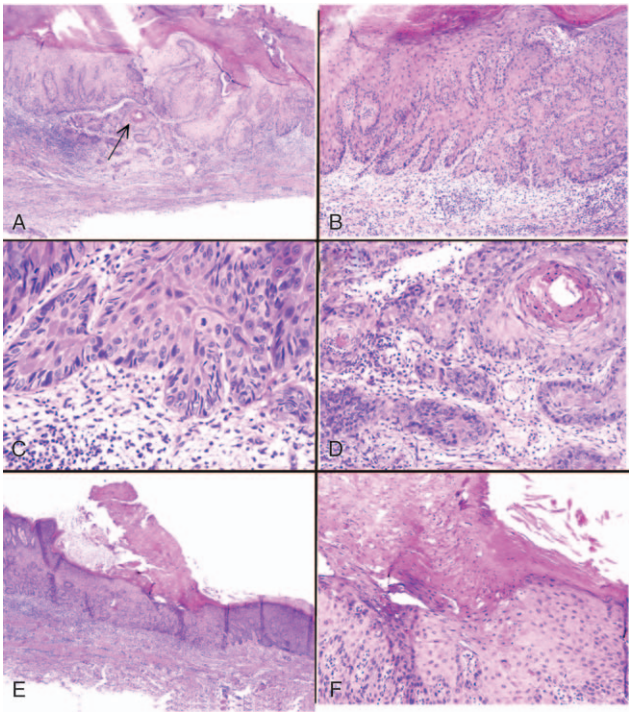

Figure 2. (A) Low magnification shows hyperkeratosis, parakeratosis, and acanthosis of the epidermis, atypical cells in the lower part of the epidermis, and basal cells. There is invasion of the dermis by epidermal masses (arrowed) (hematoxylin and eosin 40×). (B) Medium power shows acanthosis with basal cell atypia (hematoxylin and eosin 100×). (C) High power shows enlarged, irregular basal cell with hyperchromatic nuclei (hematoxylin and eosin 400×). (D) Squamous nests with nuclear pleomorphism and mitoses, conspicuous keratinization (hematoxylin and eosin 200×). (E) Low power shows a thin column of parakeratotic cells (cornoid lamella) with an absent underlying granular zone (hematoxylin and eosin 40×). (F) High power shows dyskeratotic cells in the spinous layer (hematoxylin and eosin 200×).

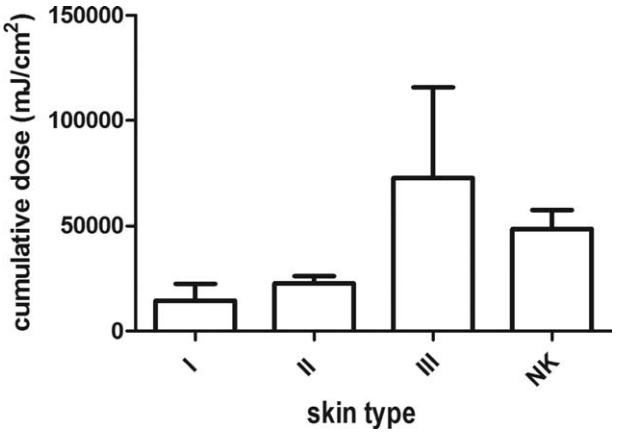

Figure 4. The relationship of Fitzpatrick skin type and cumulative dose of narrowband ultraviolet B light (NBUVB) (mJ/cm^2).

some animal studies with NBUVB.[8] However, in recent retrospective studies carried out on Asians[4] and Europeans,[2,9,10] no definite relation between NBUVB therapy and cutaneous carcinoma was found. In these retrospective studies, the patients only accepted NBUVB treatment. However, our patient received a combined therapy of IFN-α and NBUVB. IFN-α-2a may act as a photosensitizer because the cutaneous T-cell lymphomas patients who received IFN-α-2a combined with psoralen and ultraviolet A had increased the risk of skin burning.[11] Man et al[2] had revealed a small but significant increased risk of basal cell carcinoma (BCC) in patients who accepted NBUVB therapy compared with controls. But they thought that a diagnosis bias, more sunlight exposure, and the inexact exclusion criteria could explain the phenomenon. Nonetheless, in our case, the lesions located on the nonexposed area, the typical pathological changes of AK, AK with transformation of SCC, coexistence of AK, and porokeratosis

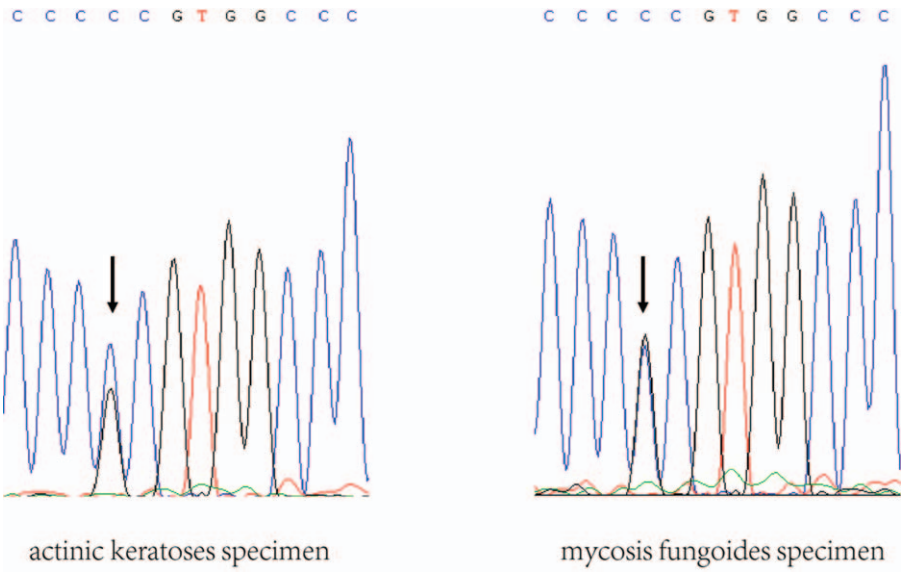

Figure 3. Polymerase chain reaction-single nucleotide polymorphism (PCR-SNP) analysis presents C–G mutation (arrowed) of exon 4 of p53 gene in the actinic keratosis and mycosis fungoides specimen.

in one sample, all of these special findings could rule out the above possibilities.

As a sensitive indicator of exposure to UV light especially UVB, AK usually presents as multiple, erythematous, dry, scaly lesions. In pathology, it displays keratinocytic dysplasia from mild changes through to carcinoma in situ. Often, SCC arises in AK, chronic ulceration, or on the margin of chronic infections and is usually nodular, ulcerated, plaque-like, or verrucous tumor. UVB caused C–T and CC–TT mutations of p53 have recently been identified in human cutaneous SCC[12] and tumor-stage MF.[13] But, these mutations are observed in AK to a significantly lesser extent in Asians than in Caucasians.[12] AK and MF specimens from our patient were chosen for the analysis of 4 to 9 exons of p53 gene because over 95% of all mutations are known to occur at these locations in human cancer.[14] Only C–G mutation in exon 4 of p53 gene was found. UV signature mutations (C–T and CC–TT) were not found in our patient's specimens. C–G transversion of p53 had 6% prevalence in skin cancer.[14] The mutation induces glycine to alanine. Because of the limited cases, the sense of the mutation is to be determined.

Porokeratosis is characterized by annular plaques with a distinct peripheral keratotic ridge clinically and cornoid lamella histologically. The etiopathogenesis of porokeratosis may include genetic factors, ultraviolet rays, immunosuppression (such as organ transplantation, MF), drugs.[15] In a retrospective study of 11 cases of porokeratosis, two-thirds of cases showed AK and carcinoma in situ in areas of porokeratosis.[16] In our case, the features of porokeratosis were found overlying the area of AK. However, we didn't find similar changes from the AK and MF lesions removed in our hospital. And, no typical lesions of porokeratosis were detected by carefully physical examination, and no family history of similar lesions. We speculated that the changes of porokeratosis were probably induced by NBUVB treatment.

To date, 15 documented cases with detailed clinical data of nonmelanoma skin carcinoma or other skin diseases after NBUVB therapy including our case have been reported.[2–6]

Table 2

Clinical and demographic data of patients with NBUVB treatment.

Parameter	Number of case, %
Age	
Mean ± SD	62.08 ± 11.78
Max	88.9
Min	51.07
Sex	
Male	10 (66.67%)
Female	5 (33.33%)
M:F	2:1
County	
Europe	11 (73.33%)
Asia	4 (26.67%)
Europe:Asia	2.75:1
Skin type	
I type	4 (26.67%)
II type	3 (20%)
III type	5 (33.33%)
NK	3 (20%)
Treatment	
NBUVB only	11 (73.33%)
NBUVB + other treatment	4 (26.67%)
Cumulative number of UVB treatments	
Mean ± SD	43.71 ± 40.10
Max	146
Min	6
Cumulative UVB dose, mJ/cm^2	
Mean ± SD	42,400 ± 58,299
Max	239,000
Min	319
Secondary skin disease	
Tumor	12 (80%)
Nontumor	2 (13.33%)
Both	1 (6.67%)

NBUVB = narrowband ultraviolet B light, NK = not known, SD = standard deviation, UVB = ultraviolet B light.

Table 1

List of reported cases of secondary skin diseases after NBUVB therapy in the literature and our case.

Source	Age, years/sex	Country	Skin type	Diagnosis	Treatment	Cumulative no. of UVB treatments	Cumulative UVB dose, mJ/cm^2	Secondary skin disease
Man et al 2005[2]	57/F	UK	II	Polymorphic light eruption	NBUVB	60	23,827	BCC
	53.37/M	UK	I	Psoriasis	NBUVB	15	3,055	BCC
	51.07/M	UK	II	Dermatitis	NBUVB	25	16,480	BCC
	78.28/M	UK	I	Psoriasis, chronic actinic dermatitis	NBUVB	10	319	BCC
	88.9/F	UK	I	Dermatitis	NBUVB	30	19,865	BCC
	66.5/M	UK	III	Psoriasis	NBUVB	54	27,228	BCC
	61.2/M	UK	II	Pityriasis lichenoides chronica	NBUVB	20	28,097	BCC
	53.4/F	UK	III	Polymorphic light eruption	NBUVB	6	777	BCC
	62.3/M	UK	III	Psoriasis	NBUVB	20	23,375	BCC
	73.2/F	UK	I	Psoriasis	NBUVB	69	34,963	BCC
Brazzelli et al 2006[3]	52/M	Italy	III	Vitiligo	NBUVB	146	239,000	Keratoacanthoma
Jo et al 2011[4]	52/M	Korea	III–V	Psoriasis	PUVA, NBUVB	26	42,400	BCC
Kwon et al 2011[5]	53/M	Korea	NK	Psoriasis	BBUVB, NBUVB	26	65,960	Pemphigus foliaceus
Kawara et al 2011[6]	75/M	Japan	NK	Psoriasis	corticosteroid and calcipotriol, NBUVB	NK	37,800	Disseminated superficial actinic porokeratosis
Our case	54/F	China	III	Mycosis fungoides	IFN-α + NBUVB	105	72,850	AK, AK with SCC transformation, Porokeratosis

AK = actinic keratoses, BCC = basal cell carcinoma, IFN-α = interferon-α, NBUVB = narrowband ultraviolet B light, NK = not known, PUVA = psoralen and ultraviolet A, SCC = squamous cell carcinoma, UK = United Kingdom, UVB = ultraviolet B light.

The clinical data of these cases were summarized in Table 1 and analyzed in Table 2. It has shown that all of the patients are more than 50 years old, and the ratio of male to female is 2:1. From the results, there may be age bias in these patients. As the patients' ages, the incidence of tumor increases. The age bias may influence the tumor incidence after NBUVB therapy. The patients with Fitzpatrick skin type III significantly got a much higher cumulative dose of NBUVB than those of type I and II (Fig. 4). Similar results were also observed by Jang et al[17] that a higher skin type was significantly less responsive to NBUVB in MF patients. The patients with lower skin type seem to be more sensitive to NBUVB and get more side effects from the therapy. However, further studies and observations are needed to determine the definite risk factors of NBUVB treatment and secondary skin diseases.

5. Conclusion

With the increasing usage of NBUVB therapy, more attention should be paid for the side effects of this regimen. To our knowledge, our case is the 1st MF patient accompanied with AK, AK with SCC transformation, and porokeratosis after NBUVB treatment. Lower Fitzpatrick skin type may be the risk factor of secondary skin diseases after NBUVB treatment. However, no definite relation between NBUVB and cutaneous carcinoma was found. Therefore, further prospective studies and long-term follow-up is still necessary for patients undergoing NBUVB treatment.

Acknowledgements

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