Original Article

A Study of Histopathological Changes Seen in Chronic Plaque Psoriasis, Before and After Treatment with Narrow Band Ultraviolet B

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ABSTRACT

Background: Psoriasis is a multifactorial chronic inflammatory skin disease characterized by infiltration of T cells in dermis and hyper proliferation of keratinocytes in epidermis. Narrow band ultraviolet B (NB UV-B) therapy utilizes the narrow band of UV light frequencies peaking around 311 – 313 nm. Very few histopathological studies have been done, especially on Asian skins which are predominantly that of Fitzpatrick type IV to V to assess the of effectiveness of narrow band ultraviolet B (NBUVB) for psoriasis.

Methods: Severity of psoriasis was graded clinically using Psoriasis area severity index (PASI) score and the Success Rate and Effective Rate of UVB therapy were calculated. Two 4 mm punch biopsies were taken before and after therapy from the affected area of the skin of each patient. Each patient was given a histopathological score based on certain histological parameters such as parakeratosis, thickness of granular layer and mitotic figures. The difference between pre and post treatment histopathological score was calculated. The changes in histopathological parameters among the responders were compared with that of non responders.

Result: Success rate of NBUVB therapy in our study was 91.52%. The mean (±SD) PASI scores before and after treatment were 12.44±2.23 and 2.83±4.49 respectively. The mean (±SD) histopathological score before and after treatment were 9.25± 0.44 and 1.81±1.93 respectively. These differences in the scores were found to be statistically significant (p<0.001).

Conclusions: A significant difference was observed between the responders and non responders in the mean change in PASI score and histopathological scores. Percentage of parakeratosis, thickness of granular layer and mitotic figures per mm of the surface can be used as markers of progression to remission following therapy.

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Introduction

Psoriasis is a multifactorial skin disease with hereditary component that affects 1%-3% of world population. It is characterized by infiltration of T cells and hyperproliferation of keratinocytes in focal skin areas. Narrow Band Ultra Violet B (NB UV-B) is a modality of phototherapy that utilizes the Narrow Band of UV light frequencies peaking around 311 – 313 nm. It has immunosuppressive properties and also inhibits cutaneous delayed type of hypersensitivity responses to haptens. Very few authors have evaluated the histopatholgical changes after the NBUVB therapy for chronic plaque psoriasis in patients with Fitzpatrick skin type IV-V [1-4].

This prospective study aims to document the histopathological changes in lesions of chronic plaque psoriasis in the tertiary care centre before and after treatment with narrow band ultraviolet B (UVB) with 30 exposures spread over the period of three months.

Materials And Methods

Source of data:

Consenting patients, clinically diagnosed to have chronic plaque psoriasis and willing to undergo NBUVB therapy at the Department of Dermatology of a teaching hospital in Bangalore, India, during the period April 2009 to March 2010, were the subjects for this study.

Method of collection of data:

This was a single centre, prospective, time bound study. The duration of study was one year from April 2009 to March 2010. Ethical clearance was obtained. The four clinical criteria used in confirming the presence of psoriasis were cutaneous plaques clinically suggesting psoriasis, bilateral symmetry of lesions, involvement of characteristic skin areas, presence of nail changes [5,6] Patients' personal particulars such as age, sex, religion and history of presenting illness, past medical/ surgical history, treatment history were recorded. The inclusion and exclusion criteria were as follows:

Inclusion criteria

- Consenting patients having chronic plaque psoriasis aged between 18 to 60 years with no co morbid illness or any medications.

Exclusion criteria

- The patients with history of photodermatitis, e.g.: Geno photodermatoses, vitiligo, history of lupus erythematosus, dermatomyositis, melanoma and non-melanoma skin cancer, diabetes mellitus ,concomitant photo sensitising drugs and topical or systemic immunosuppressive agents, currently or in the recent past.

- Pregnant women and patients who have been on any modality of therapy for psoriasis for preceding three months.

- Patients were assessed clinically thrice a week. After informed written consent, Psoriasis Area Severity Index (PASI) scoring was done as shown below [7,8].

    a. Divide the body into four areas (A): Head (H), Upper extremities (U), Trunk to groin (T), and Legs to top of buttocks (L).

    b. Generate an average score (Scale 0-4) for the Erythema (E), Induration (I), and Scale (S) for each of the 4 areas.

    (0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe)

    c. Sum scores of Erythema (E), Induration (I), and Scale (S) for each area. i.e.,

    Head (H) = $(E_H+I_H+S_H)$

    Trunk to groin (T) = $(E_T+I_T+S_T)$

    Upper extremities (U) = $(E_U+I_U+S_U)$

    Legs to top of buttocks (L) = $(E_L+I_L+S_L)$

    d. Generate a percentage for skin covered with psoriasis for each Area (A) and convert that to a 0–6 scale. (0 = 0%; 1 = <10%; 2 = 10–<30%; 3 = 30 – <50%; 4 = 50–<70%; 5 = 70–<90%; 6 = 90–100%).

    e. Multiply score of item (c) with item (d) above for each area and multiply that by 0.1, 0.2, 0.3, and 0.4 for head, arms, trunk, and legs, respectively.

    f. Add these scores to get the PASI score. i.e.,

    PASI= $0.1(E_H+I_H+S_H) A_H + 0.3(E_T+I_T+S_T) A_T + 0.2(E_U+I_U+S_U) A_U + 0.4(E_L+I_L+S_L) A_L$

PASI score from 0-72 was then calculated.

A 4mm punch biopsy was taken from the active psoriatic lesions before treatment. Patients were treated with NBUVB as per guidelines recommended for their type of skin by the British Association of Dermatology. They were reviewed thrice a week before and after each phototherapy session and the dosage increased as per the guidelines till 30 sessions were completed. A repeat punch biopsy was taken close to the site of previous biopsy.

Based on the clinical response to NBUVB, Patients were classified as "Good", "Moderate", "Mild" and "No Improvement" categories when they showed ≥90%,60% to 89%,25% to 59%,≤ 25% reduction in PASI scores respectively [Figure 1a&b].

"Effective rate" [9] = [(cases with very good improvement + cases with moderate improvement)/ total number of

cases] × 100% and "Success rate" was calculated with the formula: Success rate = [Number of improved cases / total number of cases] X 100%

The following histopathological findings were specially looked for and given score of ("0 ") when absent or ("1") when present. They include: Parakeratosis, Munro micro abscesses in keratin layers, spongiform pustules of Kogoj in epidermis, reduction or absence of granular layer, acanthosis, regular elongation of rete ridges and clubbing of their lower ends, thinning of suprapapillary epidermis, edema and distension of papillae, dilated tortuous capillaries, perivascular lymphocytes in dermis[Figure 1c] [10,11].

Ocular micrometer was used to measure the thickness of stratum malpighii, thickness of stratum granulosum, and average height of dermal papilla[12,13]. Thickness of stratum malpighii was measured starting from under surface of stratum corneum to stratum basalis at ten different high power fields in two separate sections lying at least 6 sections apart and an average was taken[12]. The height of the dermal papilla was measured starting from lowest point of rete pegs to the highest point on dermal papilla in

ten different high power fields in two histological sections lying at least six sections apart and an average was taken [12]. Estimation of mitosis: The mitotic figures were counted in all the layers of epidermis, in the histopathology sections which represented 3 mm of epidermal surface. Two sections lying at least six sections apart were utilized in determination of mitotic index. Then the average number of mitotic figures per millimeter of epidermal surface was calculated [Figure 1d][14].

Treatment Protocol: Patients were given 30 exposures of NBUVB over the period of three months, on thrice a week basis. The phototherapy unit was a whole body irradiation unit fitted with 18 Philips TL01/100W fluorescence lamps. The minimal erythema dose (MED) is first determined before treatment. All the patients belong to the Fitzpatrick skin type IV and V. The preferred MED test site was the upper back. The template was made of a thin sheet of leather with 8 windows of 2 x 2 cm with Velcro tapes stitched to the margin for manual closure of windows after each dose. Patients' upper backs were irradiated after fixing this template using a test dose ladder of 250-1500 mJ/cm^2 (250, 500, 750, 1000, 1100, 1200, 1300 and 1500). The rest
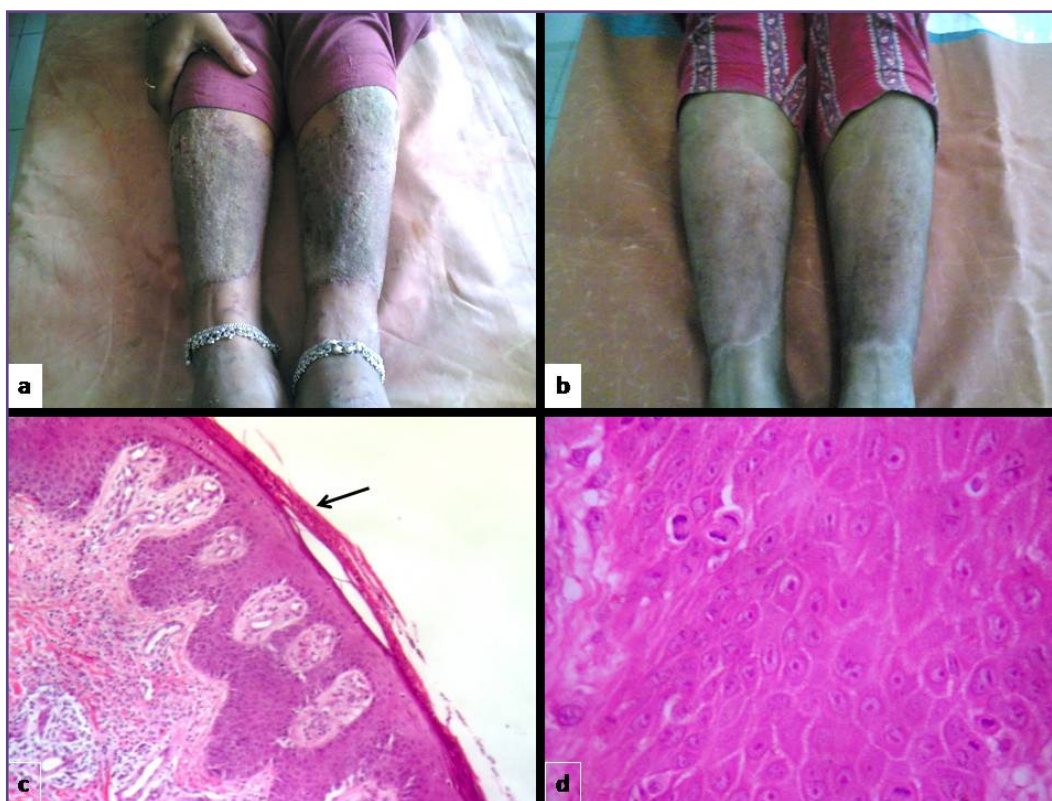

Fig. 1: showing a) Pretreatment case of chronic plaque psoriasis, b) post treatment case of chronic plaque psoriasis,c) photomicrographs showing acanthosis, papillomatosis, edema of dermal papilla, Munroe Microabscess (arrow)(H&E;x100), d)increased suprabasal mitosis (H&E;x400).

of the body was adequately protected from irradiation by using a protective gown and goggles.

MED were read at 24 hours after NBUVB exposure. A test was considered to have 1+ erythema if faint uniform erythema was present, but margination was not required. MED for NB-UVB varied from 500 to 1100 mJ/cm^2 (average 893 mJ/cm^2), and the median MED was 1000 mJ/cm^2. According to the skin type, the MEDs were 750-1100 mJ/cm^2 in type IV skin (Median , 1000 mJ/cm^2) and 500-1100 mJ/cm^2 in type V skin (Median, 750 mJ/cm^2) and the starting irradiation dose is set at 70% of MED[15]. The subsequent dosages were adjusted based on the level of erythema after previous treatment. Twenty percent dose increments were given with each subsequent exposure, till 30 exposures are completed over the period of 3 months.

This was followed by re- biopsy at the same lesion. The histopathological changes were recorded as above and compared with pre treatment histological findings. Post treatment PASI score was calculated and compared with pre treatment PASI score. PASI change value was calculated by the formula [15] , PASI change value = [(pretreatment total score of PASI – post-treatment total score of PASI)/ pretreatment total score of PASI] ×100%.

Statistical Analysis: The data collected was entered in the Microsoft excel sheet. All the statistical analyses was performed using SPSSV version 18(Statistical Package for Social Science) after importing data to SPSS. An (Alfa) error of 5% was considered to test the significance or $p < 0.05$ was considered as statistically significant. Comparison of study variables before and after treatment was done using Wilcoxson signed rank test (non-parametric test). Comparison of change produced after treatment in various study variables was done using an independent 't' test.

Result
Histological comparison of pre & post treatment biopsy specimen and PASI score: In this study a statistically significant($p<0.001$) improvement was noted following narrow band ultraviolet B therapy in PASI score, histopathological score, percentage of parakeratosis, number of mitotic figures per millimeter of surface, height of dermal papilla, thickness of granular layer and stratum malphigii[Table 1]. Patient categorization based on reduction in PASI score is shown in Table 2.

Success Rate of UVB = [Total number responders/ total number of non responders] X 100

= { [54 / 59] X 100}= 91.52%.

Effective Rate of UVB = [(number of patients with good improvement+ number of patients with moderate improvement) / total number of patients] X 100

= { [(29+23)/ 59] }X 100 = 88.1%.

Side Effects Observed After NBUVB Therapy: Itching was observed following NBUVB therapy in 2(3.38%) patients. None of the patients had a burn. The rest 57(96.61%) did not have any side effects.

Comparison of Responders and Non Responders: The patients were divided into two groups based on PASI change value as responders (those with more than 25% improvement in PASI score.) and non responders (those with less than or equal to 25% improvement in PASI score). There were 54 responders (29 cases with good improvement, 23 cases with moderate improvement, and 2 cases with mild improvement) and 5 non responders. Of the 54 improved cases 32 (59.3) were males and 22 (40.7) were females. Most of them were in 31-40 year age group. Only 5 cases were in 51-60 year age group. Most of these patients 28 (51.9%) had the disease for a duration of less than 10 years. Among the 5 non responders, there were 4 females and 1 male patient. Two patients were in the age group of 31-40 and one case each was there in remaining age groups. Two of the patients had the disease for more than 20 years, and 2 had it for less than 10 years.

A significant difference was observed between the responders and non responders in the mean change value of following variables: PASI score, histopathological score, percentage parakeratosis, thickness of granular layer, thickness of the stratum malpighii , height of dermal papilla , mitotic figures per mm of the surface[Table 4].

The percentage change observed in the PASI score, histopathological score, percentage parakeratosis, thickness of granular layer, thickness of stratum malpighii, height of the dermal papilla have shown considerably good improvement in responders as compared to non responders and therefore can be taken as reliable markers predictive of good response to therapy. Percentage reduction in mitotic figures per mm of surface is unsuitable to be used as marker to predict progression towards resolution of psoriasis following NBUVB.

Discussion
This was a prospective study conducted to evaluate the histopathology in cases of chronic plaque psoriasis and to document the changes after therapy with narrow band UVB. Basic data such as age, sex, past history, treatment history, and family history were noted down. Clinical features such as pruritis, redness, exacerbating factors were noted. Baseline PASI score was calculated followed by a skin punch biopsy which was analyzed and compared with the post treatment biopsy. All the patients were treated with 30 exposures of narrow band ultraviolet B.

Success Rate: Success rate of ultraviolet B therapy in the present study was 91.52%. The success rates were 90% and

Table 1: Clinical and histological comparison of the pre & post treatment cases.

Parameter	Pre treatment biopsy		Post treatment biopsy		Improvement		p- value	Percentage change	
	Mean	SD	Mean	SD	Mean	SD		Mean	SD
PASI score	12.44	2.23	2.83	4.49	9.61	2.94	<0.001	80.71	24.79
Histopathological score	9.25	0.44	1.81	1.93	7.44	1.63	<0.001	81.04	18.90
Percentage parakeratosis	68.39	19.37	5.95	17.85	62.44	20.72	<0.001	93.37	19.56
Mitotic figures per mm	2.96	1.33	0.81	0.64	2.15	0.87	<0.001	73.04	11.85
Thickness of stratum malpighii (µm)	448.27	123.77	140.80	77.93	307.47	117.29	<0.001	68.07	12.49
Average height of dermal papilla (µm)	425.24	127.11	113.14	84.59	312.10	121.64	<0.001	73.32	13.86
Height of granular layer in micrometer (µm)	5.05	9.16	37.66	16.06	32.61	16.10	<0.001	86.03	24.21

Table 2: Distribution of patients based on reduction in PASI score.

Group	Category	Number of cases	Percentage
Responders	Good improvement	29	49.15
	Moderate improvement	23	38.98
	Mild improvement	2	03.38
Non responders	No improvement	5	08.49
Total		**59**	**100**

Table 3: Side effects observed after NBUVB therapy.

Side effects	Number of cases	Percentage
Itching	2	3.38
Erythema	0	0
No side effects	57	96.61
Total	**59**	**100**

Table 4: Comparison of the responders and non responders based on improvement in clinical and histological parameters:.

SI.No:	Parameter	Mean change observed				Percentage change observed				p – value
		Responders (n= 54)		Non responders (n=5)		Responders (n=54)		Non responders (n=5)		
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	
1.	PASI score	10.34	1.76	1.76	0.62	87.23	12.64	10.24	3.78	<0.001
2.	Histopathological score	7.89	0.69	2.60	0.55	86.13	8.74	26.00	5.48	<0.001
3.	Percentage of Parakeratosis	65.63	18.50	28.00	8.37	99.16	2.98	30.87	9.62	<0.001
4.	Mitotic figures per mm of surface	1.98	0.70	3.92	0.38	74.29	11.57	59.53	3.39	0.001
5.	Thickness of stratum malpighii(µm)	314.80	119.54	228.40	39.89	70.88	8.55	37.80	6.26	< 0.001
6.	Height of dermal papilla(µm)	320.85	123.11	217.60	39.13	76.67	8.48	37.08	6.01	<0.001
8.	Thickness of granular layer(µm)	35.59	13.29	0.40	0.89	87.31	22.47	3.33	7.45	<0.001

86% respectively in the studies conducted by Green C [16] and Dogra S [2] et al.

Reduction Observed in PASI Score: It has been observed in this study that the mean (±SD) PASI score before treatment was 12.44±2.23 and after treatment was 2.83±4.49 with a percentage reduction of 80.71 ±24.79. This difference in the PASI score before and after treatment was found to be statistically significant (p<0.001).

Hiong and coworkers (2002) [1] treated 26 patients diagnosed with chronic plaque psoriasis with narrow band UVB therapy. The median pretreatment PASI score was 14.7 (range 4.8-30). At the end of therapy 68% patients achieved greater than 70% reduction in PASI scores. The median improvement after the completion of 20 exposures was 75% (means 71%; range 8-98%). Tanew A and colleagues (1999) [17] showed that the median pretreatment PASI score of 16 (range 6.2-23.4) was reduced by 84% to 2.5 (range 0-12.6) by narrow band UVB treatment and by 89% to 1.8 range (0-8.2) by PUVA treatment. Coven TR and coworkers [18] showed that clinical resolution of psoriasis was achieved in 86% cases treated with NBUVB. On an average disease severity scores following NBUVB were reduced by 38% after 1week, 66% after 2 weeks, 80% after 3 weeks, and 92% after 4 weeks. Picot E and colleagues (1992) [19] showed that the percentage reduction of psoriatic lesions was 78.5% with NBUVB.Thus the results of the current study are in concurrence with the results of these studies.

Grades of Improvement: In the present study 29 (49.15%) cases showed good improvement, 23 (38.98%) cases showed moderate improvement, 2 (3.38%) cases showed mild improvement, and in 5 (8.47%) there was no improvement. The effective rate was 88.13%. Yuehua Y and colleagues (2010) [9] treated 73 patients with chronic plaque psoriasis with narrow band ultra violet B and found out the change in PASI score. In their study 11 (25.6%) cases showed good improvement, 25 (58.1%) cases showed moderate improvement, 5 (11.6%) cases showed mild improvement and 2 (4.7%) cases showed no improvement. In their study the effective rate was (83.7%). Thus the results of the present study are in concurrence with the above mentioned study.

Histopathological Improvement: In the present study that the mean (±SD) histopathological score before treatment was 9.25 ± 0.44 and after treatment was 1.81 ± 1.93 with a percentage reduction of 81.04 ± 18.90. This difference in the score before and after treatment was found to be statistically significant (p<0.001).

Highest thickness of stratum malpighii observed before the therapy was 708 micrometers and lowest value was 254 micrometers. The maximum height of dermal papilla before therapy was 687 micrometers. The highest of mitotic figures prior to therapy was 7.2 per mm of epithelial surface. The maximum percentage of parakeratosis before the treatment was 95%. The highest pretreatment thickness of granular layer was 38 micrometer and lowest value was 0 (Absent granular layer). Gordon M et al [20], studied histopathological sections from 100 untreated psoriasis cases and 3 normal patients which served as controls. On the sections from psoriatic skin, the thickness of stratum malpighii varied from 242 micrometers to 448 micrometers and average was 303 micrometers. The height of the dermal papillae varied from 151 to 408 micrometers. Average was 250 micrometers. On the sections from normal skin, the distance between under surface of stratum corneum and bottom of rete ridges varied from 73-105 micrometers. The height of the dermal papillae varied from 36 to 55 micrometers. Thus the results of this study are comparable to that of above mentioned studies.

The mean (±SD) thickness of stratum malpighii before treatment was 448.27 ± 123.77 micrometers and after treatment was 140.80 ± 77.93 with a percentage reduction of 68.07±12.4. The maximal thickness of stratum malpighii in the study conducted by Soltani K [21] et al was 600 micrometers, and at that level the height of the dermal papilla was 250 micrometers, thickness of granular layer was 10 micrometers, and mitotic count was 9.0. Walters I.B and coworkers (1999) [22] treated eleven patients with narrow band UVB for 6 weeks on a three times a week basis. Mean thickness of stratum malpighii before treatment was 242.53 micrometers and following narrow band therapy was 149.66 micrometers, percentage reduction was 36.83%. UV B induced lymphocyte reduction in dermis was 45.63%. Coven TR and colleagues(1997) [18]compared the therapeutic effectiveness of daily exposure to narrow band UVB and broad band UVB employing 22 patients with chronic plaque psoriasis. Mean thickness of stratum malpighii measured 265 +/- 13.4 micrometer before and 145 +/- 10.9 micrometer after NB UVB treatment. Thus the findings of this study are comparable to other studies mentioned above.

In the present study that the mean (±SD) number of mitotic figures per millimeter of surface before treatment was 2.96 ± 1.33 and was 0.81 ± 0.64 after treatment with a percentage reduction of 73.04 ± 11.85. The mean (±SD) percentage of parakeratosis before treatment was 68.39 ± 19.37and after treatment was 5.95 ± 17.85 with a percentage reduction of

93.37 ± 19.56. Cox A.J and Watson W (1972) [23] studied histological sections from 107 cases of psoriasis. Among the 10 patients who had 0-20% parakeratosis, average mitotic figures per millimeter of the surface was 1.7 and among the 35 patients with 91-100% parakeratosis average mitotic figures per millimeter of the surface was 8.7.

In this study the mean (±SD) height of dermal papilla was 425.24 ± 127.11 micrometers and after treatment was 113.14±84.59 with a percentage reduction of 73.32 ±13.86. The mean (±SD) thickness of granular layer was 5.05 ± 9.16 micrometers and after treatment was 37.664 ± 16.06 with a percentage reduction of 86.03 ± 24.21.

Comparison of Responders and Non Responders: The clinical and histological parameters that can be used as reliable markers to identify the responders were: Percentage reduction in PASI score, percentage reduction in histopathological score, percentage reduction in percentage of parakeratosis, percentage reduction thickness of granular layer, percentage reduction in thickness of stratum malpighii, percentage reduction in height of dermal papilla.

In all these parameters the improvement observed in responders was significantly more than that seen in non responders. Percentage reduction in mitotic figures per mm of surface showed considerable improvement even in non responders; therefore cannot be used as marker to predict resolution following NBUVB therapy.

Conclusion

Majority of the patients with chronic plaque psoriasis showed "Good Improvement" following the NB UVB therapy with a very high Success Rate of 91.52% and Effective Rate of 88.1%. A significant difference was observed between the responders and non responders in the mean change of following variables: PASI score, histopathological score, percentage of parakeratosis, thickness of granular layer and mitotic figures per mm of the surface. Therefore these can be used as markers of progression to remission following therapy.

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