TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2014) 44: 89-94
© TÜBİTAK
doi:10.3906/sag-1211-18

PUVA phototherapy-induced secondary amyloidosis in patients with mycosis fungoides: a rare adverse effect of phototherapy

Itır Ebru ZEMHERİ[1,*], Sıdıka Şeyma ÖZKANLI[1], İlkin ZİNDANCI[2], Serkan ŞENOL[1], Özge AKBULAK[2], Filiz TOPALOĞLU DEMİR[2]

[1]Department of Pathology, Medeniyet University Göztepe Training and Research Hospital, İstanbul, Turkey
[2]Department of Dermatology, Medeniyet University Göztepe Training and Research Hospital, İstanbul, Turkey

Received: 06.11.2012 • **Accepted:** 05.02.2013 • **Published Online:** 02.01.2014 • **Printed:** 24.01.2014

Aim: Amyloidosis is a common disorder in adults. Secondary amyloidosis in patients with mycosis fungoides (MF) after photochemotherapy with 8-methoxypsoralen followed by ultraviolet A (PUVA) treatment has not been reported. Our aim is to describe the clinical and histological features of PUVA phototherapy-induced secondary amyloidosis.

Materials and methods: Sixty-one patients with MF treated with PUVA phototherapy were analyzed clinically and pathologically and by staining with Congo red and crystal violet.

Results: Of 61 patients, 5 met the study criteria. Secondary amyloidosis was detected in 5 patients treated with PUVA. The secondary amyloidosis appeared after a mean of 56 exposures (range: 30–81) and a mean cumulative PUVA radiation dose of 131.7 J/cm2 (range: 31–305.5). The mean follow-up duration from the date of occurrence of the secondary amyloidosis was 18.2 weeks (range: 10–30). Histologically, vacuolar interface changes, colloid bodies, and melanophages were seen in all 5 patients. There were 4 patients who had perivascular lymphocytic infiltration and 1 patient had lichenoid lymphocytic infiltration.

Conclusion: It should be noted that secondary amyloidosis can be present in patients who have been treated with PUVA therapy and it can be a result of the apoptotic effect of PUVA on the basal keratinocytes.

Key words: Secondary amyloidosis, mycosis fungoides, PUVA

1. Introduction

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma. Photochemotherapy with 8-methoxypsoralen followed by ultraviolet A (PUVA) is a well-established and effective treatment option for early-stage disease (1). One of the action mechanisms of PUVA therapy is mediated by the induction of apoptosis of both keratinocytes and lymphocytes (2).

Secondary localized cutaneous amyloidosis refers to clinically unapparent amyloid deposits within the skin. This is actually the most common type of localized cutaneous amyloidosis (3). Amyloid deposits have been observed in inflammatory dermatoses and skin tumors (4–6). There are also reports that investigated the apoptotic effect on basal keratinocytes following PUVA therapy, and the consequent enzymatically degradation of apoptotic keratinocytes to amyloid (7).

To date, secondary cutaneous amyloidosis after PUVA phototherapy in patients with MF has not been reported.

* Correspondence: ebruzemheri@gmail.com

2. Materials and methods

Between 2008 and 2011, the control biopsies of 61 patients with early-stage MF who were treated with PUVA and narrow band ultraviolet B (NBUVB) phototherapy were analyzed. The skin phototypes of all patients were classified according to the Fitzpatrick scale (types 1–6). The patients were staged by using the TNM system as stages 1a, 1b, 2a, 2b, 3, and 4. The clinical presentation of the disease was classified as classic (patch/plaque form), hypopigmented, poikilodermic, erythrodermic, folliculotropic, and pityriasis-lichenoides-chronica-like. Types of phototherapy were divided into PUVA and NUVB categories. Dosimetric parameters were recorded as number of sessions and cumulative doses.

To detect the accumulation of amyloid in papillary dermis, all biopsies were stained with crystal violet and Congo red, and accumulation of amyloid in relation to MF location was recorded as present or not.

Histologically, keratosis patterns were evaluated as normal, parakeratosis, and orthohyperkeratosis.

Epidermal changes were divided into normal, atrophic, and hyperplastic. Interface changes were classified as basal vacuolar changes and colloid bodies. Dermal inflammatory infiltration was evaluated as superficial perivascular, lichenoid, and without inflammation. In addition, dilated vessels, melanophages, extravasations of erythrocytes, and fibrosis were histologically evaluated.

3. Results

The mean age of the patients (32 women and 29 men) was 50 years, ranging from 23 to 73 years. According to the Fitzpatrick scale, the observed skin types were as follows: type 1 in 5 patients, type 2 in 19 patients, type 3 in 21 patients, type 4 in 12 patients, and type 5 in 4 patients. There were 53 patients in stage 1B, 5 patients in stage 1A, and 3 patients in stage 2A. Clinically, 53 cases were of the classic type, 3 cases of the poikilodermic type, 2 cases of the folliculotropic type, 2 cases of the hypopigmented type, and 1 case of the pityriasis-lichenoides-chronica-like type of MF. The type of phototherapy was PUVA in 34 patients and NBUVB in 27 patients. The mean number of exposures was 42 (range: 30–81) and the mean cumulative radiation dose was 59.5 J/cm^2 (range: 25–305.5). The mean follow-up duration was 15.4 weeks (range: 10–30).

After phototherapy, secondary cutaneous amyloidosis was detected in 5 out of 61 patients with MF. All patients with secondary cutaneous amyloidosis were treated with PUVA. Their clinical data and treatment are summarized in Table 1. The group included 2 male and 3 female patients, with a mean age of 53 years (range: 39 and 73). There were 4 patients with skin type 2, and 1 had skin type 1. There were 3 patients who had a classic variant of MF and 2 patients who had a poikilodermic variant of MF. None of the patients experienced a photoallergic reaction during PUVA phototherapy. Clinically, brownish macules and plaques of varying diameter with pruritus were seen in all patients (Figure 1). These clinical findings were restricted to the MF lesions in all patients. The secondary amyloidosis appeared after a mean of 56 exposures (range: 30–81) and the mean cumulative PUVA radiation dose was 131.7 J/cm^2 (range: 31–305.5). The mean follow-up duration from the date of occurrence of the secondary amyloidosis was 18.2 weeks (range: 10–30). The clinical data and treatments are summarized in Table 1.

Table 1. Background data of mycosis fungoides patients. Cases of accumulated amyloid shown in bold font.

No.	Age/ sex	Phototype	Stage	Clinical variant	Type of phototherapy	PUVA/ NBUVB exposures	Total cumulative dose (J/cm^2)	Time from treatment (weeks)	Accumulation of amyloid
1	35/F	2	1B	Classic	PUVA	30	55	15	No
2	39/M	3	1B	Classic	PUVA	35	67.5	17	No
3	56/F	3	1B	Classic	PUVA	60	50.5	30	No
4	43/F	2	1B	Classic	PUVA	30	48.5	12	No
5	67/M	2	2A	Classic	PUVA	30	50	10	No
6	54/F	3	1B	Classic	NBUVB	60	69	34	No
7	71/M	4	2A	Classic (CD30+ large cell transformation)	PUVA	58	98	24	No
8	43/M	5	1B	Classic	NBUVB	60	60	30	No
9	47/F	1	1B	Classic	PUVA	40	65	15	No
10	54/F	3	1B	Classic	PUVA	30	48	10	No
11	61/F	4	1B	Classic	NBUVB	50	55	20	No
12	26/M	2	1A	Hypopigmented	NBUVB	30	26.5	10	No
13	43/F	4	1B	Classic	PUVA	30	51	20	No
14	71/M	5	1B	Classic	NBUVB	45	48.5	16	No
15	48/F	4	1B	Folliculotropic	PUVA	45	68	15	No
16	55/M	3	1B	Classic	PUVA	30	52	10	No
17	29/F	3	1B	Classic	PUVA	30	52	10	No
18	**68/F**	**2**	**1B**	**Poikilodermic**	**PUVA**	**81**	**118.5**	**16**	**Yes**
19	53/F	2	2A	Classic (CD30+ large cell transformation)	PUVA	65	116.5	23	No

Table 1. (Continued).

20	56/M	3	1B	Classic	NBUVB	45	50	15	No
21	**39/F**	**2**	**1B**	**Classic**	**PUVA**	**79**	**305.5**	**30**	**Yes**
22	63/F	3	1B	Classic	PUVA	30	48.5	10	No
23	55/F	4	1B	Classic	PUVA	40	65	14	No
24	56/F	3	1B	Classic	PUVA	40	63	14	No
25	48/M	4	1B	Classic	PUVA	30	50	10	No
26	61/M	3	1B	Classic	NBUVB	30	26.5	10	No
27	53/F	4	1A	Classic	NBUVB	30	26.5	10	No
28	47/F	3	1B	Classic	NBUVB	30	26.5	10	No
29	61/F	2	1B	Classic	NBUVB	30	25	10	No
30	**73/M**	**2**	**1B**	**Classic**	**PUVA**	**30**	**31**	**10**	**Yes**
31	47/M	3	1B	Classic	NBUVB	60	65.5	24	No
32	52/F	4	1A	Classic	NBUVB	60	62	20	No
33	67/M	2	1B	Poikilodermic	PUVA	60	71	20	No
34	63/M	1	1B	Classic	PUVA	30	48	10	No
35	29/F	2	1B	Hypopigmented	NBUVB	30	26.9	12	No
36	41/F	3	1B	Classic	NBUVB	40	41.5	14	No
37	43/M	4	1B	Pityriasis-lichenoides-chronica-like	PUVA	40	65	14	No
38	68/F	1	1B	Classic	NBUVB	30	26.9	12	No
39	58/M	2	1B	Classic	NBUVB	30	26	10	No
40	23/M	3	1B	Classic	NBUVB	30	26.5	10	No
41	33/M	4	1B	Classic	PUVA	30	50	10	No
42	39/F	5	1B	Classic	PUVA	45	70.5	15	No
43	46/M	3	1B	Classic	PUVA	40	63.5	12	No
44	33/M	2	1B	Classic	PUVA	30	55	10	No
45	58/F	4	1B	Classic	PUVA	30	57	10	No
46	43/F	2	1B	Classic	NBUVB	30	25	10	No
47	**39/M**	**2**	**1B**	**Poikilodermic**	**PUVA**	**30**	**68**	**10**	**Yes**
48	70/M	3	1B	Classic	PUVA	40	65	13	No
49	45/F	3	1B	Classic	PUVA	30	55	10	No
50	29/M	2	1A	Classic	NBUVB	30	25.5	10	No
51	24/M	2	1B	Classic	NBUVB	60	62.5	28	No
52	65/M	3	1B	Classic	NBUVB	60	67.5	30	No
53	62/F	4	1B	Classic	NBUVB	30	28.7	12	No
54	61/M	3	1B	Folliculotropic	PUVA	60	115	24	No
55	49/F	2	1B	Classic	NBUVB	40	39.5	13	No
56	51/M	1	1B	Classic	NBUVB	40	40	13	No
57	54/M	2	1B	Classic	PUVA	60	105	24	No
58	29/F	4	1A	Classic	NBUVB	30	29.9	10	No
59	54/M	5	1B	Classic	NBUVB	45	46	15	No
60	53/F	3	1B	Classic	NBUVB	45	48.4	15	No
61	**46/F**	**1**	**1B**	**Classic**	**PUVA**	**60**	**135.5**	**25**	**Yes**

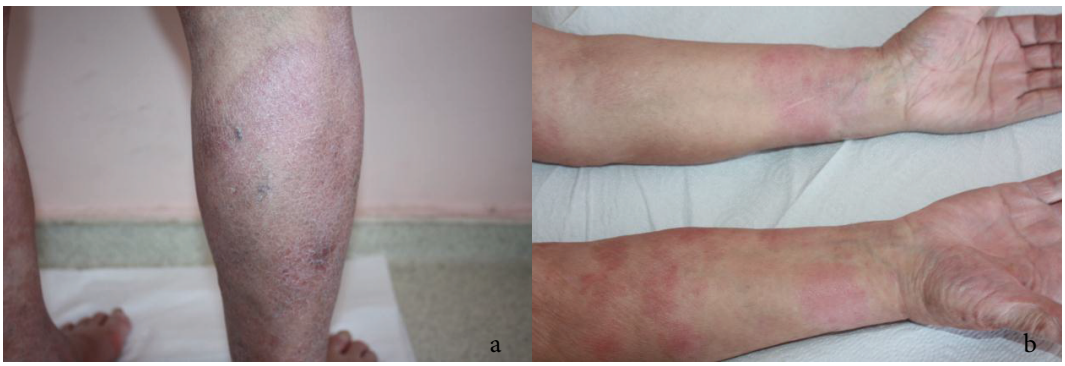

Figure 1. a) Patient no. 21, b) patient no. 30: brownish macules and plaques of varying diameter in areas previously involving mycosis fungoides.

On histopathological evaluation, normal keratosis was seen in 2 cases, parakeratosis in 1 case, and orthohyperkeratosis in 2 cases. The epidermis was atrophic in 4 cases and hyperplastic in 1 case. In all 5 cases, basal vacuolar degeneration and colloid bodies were seen in the epidermis, and dilated vessels, melanophages, and fibrosis were detected in dermis (Figure 2). Extravasated erythrocytes were seen in 3 cases, perivascular lymphocyte infiltrations were seen in 4 cases, and lichenoid infiltration was seen only in 1 case. When stained with crystal violet and Congo red, an accumulation of amyloid in the papillary dermis was seen in all 5 patients (Figure 3). The data are summarized in Table 2.

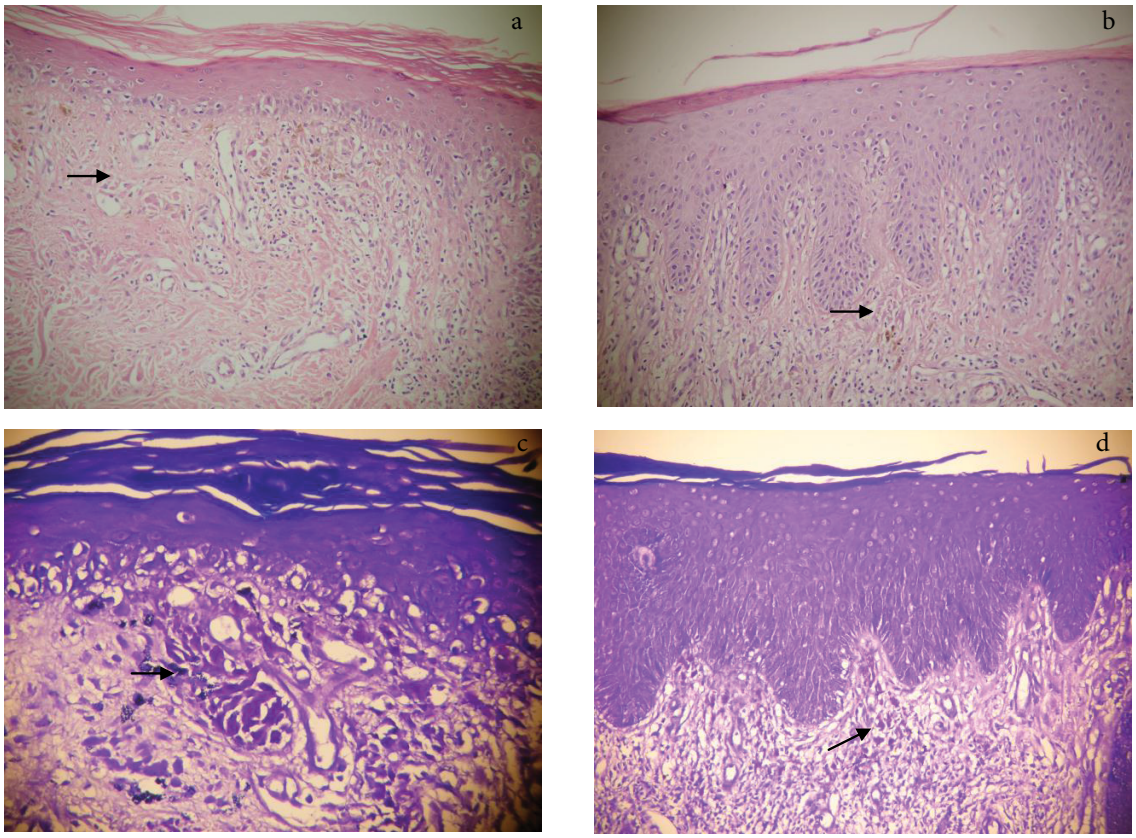

Figure 2. a) Patient no. 21: amyloid accumulation (arrow), epidermal atrophy, basal vacuolar degeneration, melanophages, and atypical lymphocytes in the upper dermis (H&E, 20×); b) patient no. 30: hyperplastic epidermis and amyloid accumulation (H&E, 20×); c, d) secondary amyloidosis (arrows) (crystal violet).

Table 2. Histomorphological parameters in patients with secondary amyloidosis.

Histopathologic findings	N (5)	%
Keratosis pattern		
Normal	2	40
Parakeratosis	1	20
Orthohyperkeratosis	2	40
Epidermal changes		
Normal	0	0
Atrophic	4	80
Hyperplastic	1	20
Interface changes		
Vacuolar change	5	100
Colloid bodies	5	100
Dermal inflammatory infiltrate		
Superficial perivascular	4	80
Lichenoid	1	20
No inflammation	0	0
Other dermal cells		
Dilated vessels	5	100
Extravasated erythrocytes	3	60
Melanophages	5	100
Fibrosis	5	100

4. Discussion

Amyloidosis can be subdivided into cutaneous amyloidosis and systemic amyloidosis with cutaneous involvement (8,9). Precipitations of amyloid were seen in the extracellular space of the dermis in both groups. In cutaneous amyloidosis, amyloid accumulates in the papillary dermis, whereas in systemic amyloidosis with cutaneous involvement, it accumulates in subpapillary layers, dermal appendages, and blood vessels (10,11).

Secondary amyloid deposition may be found in association with skin tumors (basal cell carcinoma, actinic keratoses, squamous cell carcinoma, and skin appendage tumors) and benign lesions (e.g., seborrheic warts), solar elastosis, collagenoses (e.g., lupus erythematosus), and PUVA therapy (12–17).

PUVA therapy is a mainstay in the treatment of patients with psoriasis vulgaris, cutaneous T-cell lymphoma, and several other inflammatory skin diseases (18). The mechanism of PUVA is phototoxic reactions that are the result of direct cellular damage caused by an inflammatory, nonimmunological mechanism (18). PUVA primarily targets DNA (19). Other important targets of psoralens are specific receptors, and in particular the epidermal growth factor receptor (20). However, there are also effects on other cell membrane components (21). More recently, it has been noticed that PUVA therapy can induce programmed cell death (apoptosis) in skin-infiltrating T-helper lymphocytes and keratinocytes, and so it can cause interface changes (22). There are 2 cell types found in the epidermis and dermis within the interface changes. These are melanophages and colloid bodies. Melanophages are dermal phagocytic cells of macrophage lineage that are able to engulf large amounts of melanin pigment released from epidermal basal layer keratinocytes and melanocytes that have been damaged by the interface change. Colloid bodies are thought to represent injured basal layer keratinocytes that have undergone amyloid degeneration (23,24).

Cytokeratin 5 is predominantly found in basal keratinocytes (25,26). In the pathogenesis of amyloidosis, a commonly accepted theory is that the apoptotic basal keratinocytes (colloid bodies) release cytokeratins, which are then covered with autoantibodies, phagocytized by macrophages, and enzymatically degraded to amyloid K (keratin-associated amyloid). It is a key feature of organ-limited cutaneous amyloidosis (7,25,27). Based on these results, antibodies against cytokeratin 5 may be used for diagnosing amyloidosis (7).

We detected amyloidosis in skin biopsies taken from 5 patients with MF treated with PUVA. In all of the cases with amyloid deposits, we observed interface dermatitis characterized by basal vacuolar changes, colloid bodies, and melanophages. In our patients, changes accompanying the amyloid depositions were consistent with those, as mentioned in the literature, that are seen after PUVA treatment.

In our cases, exposure to PUVA and cumulative doses showed differences. Although this leads us to the conclusion that the development of amyloid depositions are not related to the dosage or to the duration of the treatment, we think that we should not make a definite comment on this since our cases are few in number.

The age of our patients with amyloid deposits ranged from 39 to 73. In their report about amyloid deposition after psoriasis therapy with PUVA, Grene and Cox found that the ages of their patients ranged from 35 to 80, which parallels the findings in our study (28).

In addition to amyloid changes, in most of our cases, we observed epithelial atrophy, perivascular lymphocyte infiltration in the dermis, extravasated erythrocytes, fibrosis, and dilated vessels. In the literature, it was reported that hyperkeratosis, hypergranulosis, variable acanthosis, and epidermal atrophy could be seen in treatment with UV (29,30).

Clinical presentation of the effects of amyloidosis varies. Organ-limited cutaneous amyloidosis often shows yellowish or brownish macules, papules, or plaques, whereas systemic amyloidosis often initially presents with petechiae, ecchymosis, and nonhealing ulcers. These differences are due to the localization of amyloid deposition. Organ-limited cutaneous amyloidosis occurs in the papillary dermis, whereas systemic amyloidosis affects the perivascular area in the deeper dermis. Perivascular amyloid deposition in systemic amyloidosis makes blood vessels fragile, causing intracutaneous micro- and macrohemorrhages (7). In our patients, we detected brownish maculae as seen in organ-limited cutaneous amyloidosis.

On the basis of the results from our study, there was an association between PUVA treatment and secondary cutaneous amyloidosis. The association may occur frequently, but it may go unreported because the amyloid deposits may not be evident when stained with the usual stains, and also because the clinical findings are not apparent enough.

References

1. Baron ED, Stevens SR. Phototherapy for cutaneous T-cell lymphoma. Dermatol Ther 2003; 16: 303–10.
2. Morita A, Werfel T, Stege H, Ahrens C. Evidence that singlet oxygen-induced human T-helper cell apoptosis is the basic mechanism of ultraviolet-A radiation phototherapy. J Exp Med 1997; 186: 1763–8.
3. Nasser N, Sassevılle D. Amyloidosis. Dermatol Rounds 2005; 4: 3.
4. Buxbaum JN, Tagoe CE. The genetics of the amyloidoses. Ann Rev Med 2000; 51: 543–69.
5. Picken MM. The changing concepts of amyloid. Arch Pathol Lab Med 2001; 125: 38–43.
6. Falk RH, Comenzo RL, Skinner M. The systemic amyloidoses. N Engl J Med 1997; 337: 898–909.
7. Schreml S, Szeimies RM, Vogt T, Landthaler M, Schroeder J, Babilas P. Cutaneous amyloidoses and systemic amyloidoses with cutaneous involvement Eur J Dermatol 2010; 20: 152–60.
8. Breathnach SM. Amyloid and amyloidosis. J Am Acad Dermatol 1988; 18: 1–16.
9. Glenner GG. Amyloid deposits and amyloidosis. The beta-fibrilloses (first of two parts). N Engl J Med 1980; 302: 1283–92.
10. Kumakiri M, Hashimoto K. Histogenesis of primary localized cutaneous amyloidosis: sequential change of epidermal keratinocytes to amyloid via filamentous degeneration. J Invest Dermatol 1979; 73: 150–62.
11. Li WM. Histopathology of primary cutaneous amyloidoses and systemic amyloidosis. Clin Dermatol 1990; 8: 30–5.
12. Brownstein MH, Helwig EB. Secondary systemic amyloidosis: analysis of the underlying disorders. South Med J 1971; 64: 491–6.
13. Hashimoto K, Brownstein MH. Localized amyloidosis in basal cell epitheliomas. Acta Derm Venereol 1973; 53: 331–9.
14. Hashimoto K, Kumakiri M. Colloid-amyloid bodies in PUVA-treated human psoriatic patients. J Invest Dermatol 1979; 72: 70–80.
15. MacDonald DM, Black MM. Secondary localized cutaneous amyloidosis in melanocytic naevi. Br J Dermatol 1980; 103: 553–6.
16. Powell AM, Albert S, Bhogal B, Black MM. Discoid lupus erythematosus with secondary amyloidosis. Br J Dermatol 2005; 153: 746–9.
17. Ramírez-Santos A, Suárez-Amor O, Pérez-Pérez L, Loureiro M, Peteiro C, Toribio J. Localized cutaneous amyloidosis secondary to porokeratosis: a retrospective histopathologic study of 30 patients. Actas Dermosifiliogr 2008; 99: 639–43 (article in Spanish with English abstract).
18. Johansen JD, Frosch PJ, Lepoıttenvın JP. Contact Dermatitis. Berlin: Springer; 2011. p.155–62
19. Dall'Acqua F, Vedaldi D, Bordin F, Rodighiero G. New studies on the interaction between 8-methoxypsoralen and DNA in vitro. J Invest Dermatol 1979; 73: 191–7.
20. Laskin JD, Lee E, Laskin DL, Gallo MA. Psoralens potentiate ultraviolet light-induced inhibition of epidermal growth factor binding. Proc Natl Acad Sci USA 1986; 83: 8211–5.
21. Zatebsku Z. Cell membrane, a target for PUVA therapy. J Photochem Photobiol B 1994; 23: 101–9.
22. Coven TR, Walters IB, Cardinale I, Krueger JG. PUVA-induced lymphocyte apoptosis: mechanism of action in psoriasis. Photodermatol Photoimmunol Photomed 1999; 15: 22–7.
23. Sontheimer RD. Lichenoid tissue reaction/interface dermatitis: clinical and histological perspectives. J Invest Dermatol 2009; 129: 1088–99.
24. Karadağ AS, Güler Şimşek G. Familial amyloidosis cutis dyschromica. Turk J Med Sci 2010; 40: 151–4.
25. Chang YT, Liu HN, Wang WJ, Lee DD, Tsai SF. A study of cytokeratin profiles in localized cutaneous amyloids. Arch Dermatol Res 2004; 296: 83–8.
26. Miura Y, Harumiya S, Ono K, Fujimoto E. Galectin-7 and actin are components of amyloid deposit of localized cutaneous amyloidosis. Exp Dermatol 2013; 22: 36–40.
27. Hashimoto K, Ito K, Taniguchi Y, Yang F, Youngberg G. Keratin in cutaneous amyloidoses. Clin Dermatol 1990; 8: 55–65.
28. Grene I, Cox AJ. Amyloid deposition after psoriasis therapy with psoralen and long-wave ultraviolet light. Arch Dermatol 1979; 115: 1200–2.
29. Crowson AN, Magro CM. Recent advances in the pathology of cutaneous drug eruptions. Dermatol Clin 1999; 17: 537–60.
30. Epstein JH. Phototoxicity and photoallergy. Semin Cutan Med Surg 1999; 18: 274–84.