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Comparison of the efficacy and safety of intralesional injection of tranexamic acid and the topical application of Kligman combination drug in the treatment of macular amyloidosis

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Abstract

Macular amyloidosis (MA) is a common form of cutaneous amyloidosis that manifests as dark spots consisting of brown pigments with a rippled pattern on the skin, and the treatment of this condition is highly challenging. The aim of this study was to compare the efficacy and safety of intralesional injection of tranexamic acid (TXA) and topical application of Kligman combination drug in the treatment of macular amyloidosis. In this double-blind clinical trial, a total of 43 patients, who were diagnosed with MA, were treated with two different methods of intralesional injection of tranexamic acid and topical application of Kligman combination drug. Both therapeutic methods were effective in improving MA and significantly reduced hyperpigmentation of the treated areas, but tranexamic acid was significantly more effective than the Kligman combination drug. Significantly, greater improvements were observed in the group of patients treated with tranexamic acid. In the tranexamic acid treatment group, ΔE was reduced from 11.39 in the first session to 8.53 in the third session, and in the Kligman treatment group, it was reduced from 8.79 in the first session to 6.32 in the third session ($p < 0.05$). In addition, the pruritus score in patients treated with topical tranexamic acid injection was lower compared to the patients treated with the topical application of the Kligman combination drug. The results of this study demonstrated the significant positive effects of both treatment methods, but in terms of reducing melanin content, intralesional injection of tranexamic acid was a more effective method. Both treatments considered safe for MA. In tranexamic acid group, patients logically experienced a tolerable pain during injection but they significantly had significantly lower local pruritic discomfort during study. So, based on the positive findings of this study we suggest to use tranexamic acid in combination with other effective therapeutic methods for treatment of MA especially use of its topically applied form in combination with non-aggressive needling that results in better drug delivery without the experience of injection pain. Selection of the best administration route of tranexamic acid for hyper-

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pigmented lesions depends on the each patient characteristic and their previous theraputic results that may vary case by case.

KEYWORDS
cutaneous amyloidosis, hydroquinone, hyperpigmentation, Kligman, macular amyloidosis, melanosis, tranexamic acid

1 | INTRODUCTION

Macular amyloidosis (MA) is a common form of primary cutaneous amyloidosis that manifests as dark spots consisting of brown pigments with a rippled pattern on the skin. Extracellular deposition of autologous proteins is the morphological feature of amyloid fibrils.[1–3] MA is more common in women and may be acquired or inherited.[4,5] The disease is more prevalent in East Asia, the Middle East, and Central and South America thaninother regions.[6,7]

The use of Kligman topical ointment with the new formula is the most common topical treatment for these patients.[5] In fact, the hydroquinone in this compound, by inhibiting the synthesis of RNA and DNA and thus inducing the destruction of melanocytes and the decomposition of melanosomes, effectively leads to the clarification of various pigmented skin lesions.[8] However, hydroquinone-based creams have not yet been introduced as an effective treatment for MA.

Another drug that has recently been suggested for the treatment of macular amyloidosis is tranexamic acid. Tranexamic acid is a synthetic derivative of the amino acid lysine, which is primarily used to prevent or treat hemorrhage and to control menorrhagia.[9] Tranexamic acid has an effective role in reducing skin aging.[10] The use of tranexamic acid in the treatment of melasma has recently been studied,[11] but the effectiveness of this medication in the treatment of macular amyloidosis has not been investigated.

The role of the Kligman formula and tranexamic acid in the clearance of amyloidosis deposits has not been elucidated, but we hypothesize that these medications are likely to improve amyloid spots by affecting the amyloid filaments associated with melanosome-containing vesicles in a mechanism similar to melasma.

In addition to complications such as severe pruritus, MA also affects the beauty and mental health of patients, and the treatment of this condition is highly challenging.[2,12] Depending on the clinical presentation, different surgical and non-surgical treatment strategies have been proposed for this disease, and recently, the use of laser-based methods in some cases has demonstrated good results; however, despite the treatment options available, treatment of cutaneous diseases is often frustrating, and there is also a great possibility of recurrence.[13,14]

The above-mentioned points indicate the importance of providing an effective method to improve MA, which requires a multifaceted and specialized approach to identify new treatment strategies. Due to the importance of recognizing new treatment methods, the present study was performed to compare the efficacy and safety of intralesional injection of tranexamic acid and the topical application of Kligman combination drug in the treatment of macular amyloidosis.

2 | MATERIALS AND METHODS

2.1 | Study design

This double-blind clinical trial was performed in 2018–2019 in the dermatology clinic of Rasool Akram Medical Complex affiliated with Iran University of Medical Sciences. The study population included patients with macular amyloidosis skin lesions who were eligible for the study. Patients were entered into the study using the available sampling method, and written consent was obtained from all cases. This study was approved by the institutional ethics committee of the Rasool Akram Hospital (approval number: IR.IUMS.FDM.REC.1398.138).

2.2 | Inclusion and exclusion criteria

Patients with macular amyloidosis of the scapula and arm aged 18–50 years, who were satisfied with the study procedure, were included in the study. Exclusion criteria included a history of treatment with anti-pigmentation drugs such as Kligman drug during the last 3 months, pregnancy or lactation, concomitant use of anticoagulants, history of any allergies to the drugs studied, history of recent bleeding for any reason, concomitant hormone therapy or concomitant use of contraceptives, and patients with chronic diseases such as cardiovascular diseases. Also, patients who had used topical treatments containing corticosteroids, exfoliators, or brighteners in the studied areas during the last 3 months were excluded from the study.

2.3 | Random selection and blinding

Patients were divided into two groups according to a random list generated using the relevant software, based on the randomized block design in volume 4. In order to maintain the randomization process, the physician who evaluated the patients at each follow-up was blind

to the study. In addition, the data analyzer was unaware of patient grouping. Hence, the above study was a double-blind trial.

2.4 | Therapeutic interventions

Intralesional injection of tranexamic acid and topical application of Kligman combination drug was performed for 12 weeks in both groups. In the group of intralesional injection of tranexamic acid, six sessions of treatment were performed every 2 weeks. At each session, 4 mg/ml of tranexamic acid solution was injected intradermally with a 30-G needle at a depth of 1 cm, at each point 0.1 cc with a width of 10 by 10 cm that covered the entire area of the lesion. Ampoules inside the lesion were used for intralesional injections.

In the Kligman group, the Kligman drug (with the formula: hydroquinone 4.0%, tretinoin 0.05%, fluocinolone acetonide 0.01%, vitamin C 500 mg) was given to the patient and the patient was instructed to topically apply a tip of a finger of the ointment, once a night, on the dry and clean skin of the area to be completely absorbed, and the treatment area should not be washed for at least 4 h after use. The patient was also told to keep the ointment in the refrigerator.

Patients were evaluated in terms of response to treatment, 4, 8, and 12 weeks after the start and 3 months after the end of treatment, and were compared with their initial condition (day zero). For this purpose, in each session, patients were evaluated using three methods: (1) Using a VisioFace device with a 12-megapixel CANON camera (VisioFace 1000D, Germany), patients' lesions were photographed from a distance of 30 cm. In addition to photography, the ΔE (difference in hyperpigmentation compared to day zero) that was calculated by the camera was also recorded. (2) The opinion of the patients or their companions was asked about their improvements in each session (Table 1). Since the patient himself could not assess the lesions on his back and shoulders, this assessment was performed by the patient's companion. It should be noted that the patient was accompanied by one person in all sessions. The scoring scale that will be introduced in the following was used for the evaluation of the patients. The patient and his companion were also asked about side effects. (3) Evaluation by a third physician: The third physician was a dermatologist who did not know the grouping of the patients.

Due to the fact that distinguishing MA from other pigment disorders such as pigmented lichen plan may be difficult based on their clinical manifestations, the diagnosis of MA was made clinically through skin sampling by a dermatologist.

The evaluations were performed by the patient's companion and the third physician using a5-level scale[15]: No response: no improvement, poor response: less than 25% recovery, moderate response: 25%–50% recovery, good response: 50 to recovery 75%, and very good response: more than 75% recovery.

2.5 | Data collection

At the beginning of the study, patients' demographic characteristics were recorded in pre-designed questionnaires (Table 2). At the same

TABLE 1 The opinion of the patients' companions on the rate of improvement

Parameters	Items	Tranexamic acid	Kligman combination drug	*p*
Rate of improvement in the first session	No improvement	3	5	0.04
	<25%	9	15	
	25%–50%	9	2	
	50%–75%	12	7	
	Total	21	22	
Rate of improvement in the second session	No improvement	0	3	0.062
	<25%	2	7	
	25%–50%	16	10	
	50%–75%	3	2	
	Total	21	22	
Rate of improvement in the third session	No improvement	0	4	0.11
	<25%	1	6	
	25%–50%	7	7	
	50%–75%	13	5	
	Total	21	22	
Rate of improvement in the fourth session	No improvement	0	4	0.23
	<25%	1	6	
	25%–50%	8	5	
	50%–75%	12	7	
	Total	21	22	

stage and in each follow-up session, the patients' disease status was recorded. Also, in another form, the time of onset and continuation of the therapeutic effects as well as side effects were recorded by the study physician.

The per-protocol analysis method was used, due to the possibility of exclusion of patients. This means that only patients who completed their treatment and were present in all follow-up sessions were included in the analysis.

2.6 | Data analysis

After data collection, data analysis was performed by SPSS software version 21. Quantitative and qualitative data were described using Mean ± SD and relative frequency, respectively. *T*-test and Chi-square test were used to compare the groups. If the normal distribution was established, the data were analyzed using the *T*-test and if a normal distribution was not established, comparisons between groups were performed using Mann–Whitney *U* and Wilcoxon tests. *p* values less than 0.05 were considered significant.

TABLE 2 Demographic findings and frequencies

Parameters	Mean	Min	Max
Age	36.5 ± 7.91	18	51
Parameters		**Frequency**	**Percentage**
Location of MA	Right arm	11	25.6
	Left arm	18	41.9
	Back	14	32.5
	Total	43	100.0
History of disease	Yes	11	25.6
	No	32	74.4
	Total	43	100.0

3 | RESULTS

A total of 43 patients were studied; the mean age of patients was 36.5 ± 7.91 years and all of them were female. Examination of the location of macular amyloidosis showed that in 25.6% of cases, lesions were seen on the right arm, in 41.9% of cases on the left arm, and in 32.5% of patients, lesions were observed on their back. A study of the disease history showed that 25.6% of cases had a history of infection and the rest had no previous history of the disease.

Examination of the companions' opinion in terms of the effectiveness of therapeutic methods showed that the improvements were significant in both groups, but the tranexamic acid group showed a higher improvement than Kligman, and according to the opinion of the patient's companions, the recovery after the first treatment session was significant ($p < 0.05$).

Examination of the physician's opinion on the rate of improvement in the treatment groups showed (Table 3) that both groups had significant improvements in all follow-up sessions, in comparison with day zero ($p < 0.05$). Data analysis showed that both drugs were effective in the treatment of MA and caused improvements in the treated areas, but the tranexamic acid group showed a higher rate of improvement compared to the Kligman group ($p < 0.05$). Figure 1 shows the

TABLE 3 The opinion of the evaluation physician on the rate of improvement

Parameters	Item	Tranexamic acid	Kligman combination drug	*p*
Rate of improvement in the first session	No improvement	0	5	0.003
	<25%	6	13	
	25%–50%	14	4	
	50%–75%	1	0	
	Total	21	22	
Rate of improvement in the second session	No improvement	0	4	0.039
	<25%	6	11	
	25%–50%	13	6	
	50%–75%	2	1	
	Total	21	22	
Rate of improvement in the third session	No improvement	2	10	0.008
	<25%	10	10	
	25%–50%	9	2	
	50%–75%	21	22	
Rate of improvement in the fourth session	No improvement	0	11	0.000
	<25%	11	9	
	25%–50%	10	2	
	50%–75%	21	22	

recovery course of the patients of both treatment groups in four time periods.

The frequency of pain, irritation, pruritus, and bruising were different in the two groups (Table 4), but the difference was not statistically significant between the two groups ($p > 0.05$). The amount of pain was lower in the Kligman group; but the amount of pruritus, irritation, and scaling in patients treated with tranexamic acid injection was lower than patients in the Kligman group, and in terms of scaling, the tranexamic acid injection was significantly safer than the topical application of Kligman combination drug ($p < 0.05$).

The examination of hyperpigmentation in the tranexamic group showed that ΔE1 was equal to 12.05, ΔE2 was 9.92, ΔE3 was 7.97 and ΔE4 was equal to 7.10; this examination in the Kligman group showed that ΔE1 was 8.69, ΔE2 was 8.15, ΔE3 was 6.90 and ΔE4 was equal to 6.92. The difference between the two groups in terms of hyperpigmentation was statistically significant ($p > 0.05$). The above findings can be seen in Figure 2.

The separate evaluation of the effect of treatment on the studied groups showed that the differences in hyperpigmentation at different time intervals were significant in both groups (Table 5). This finding

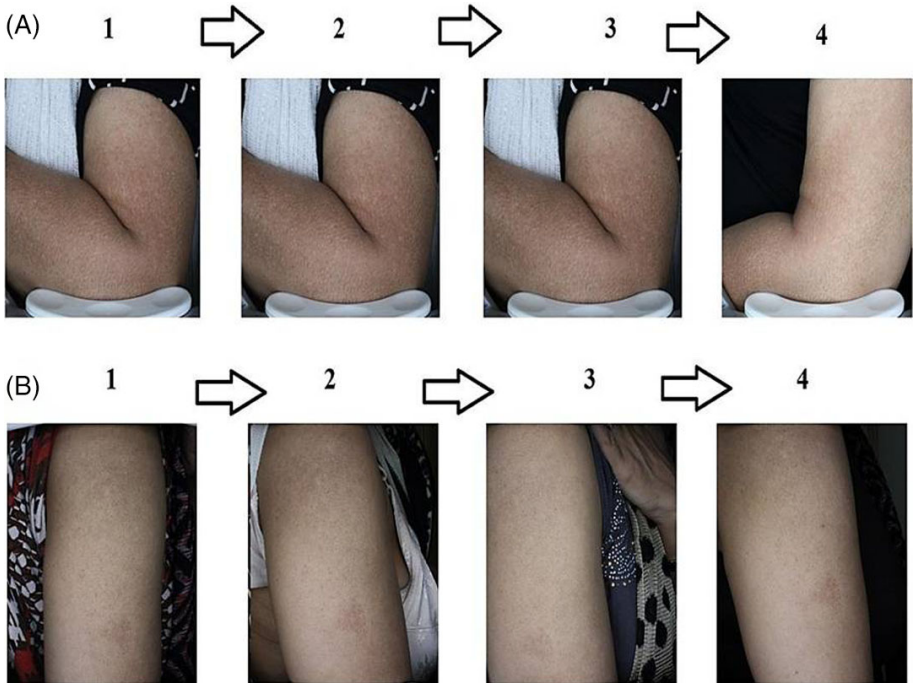

FIGURE 1 Recovery course of patients in both treatment groups (Kligman combination drug and tranexamic acid) in four sessions. (A, B) The course of recovery of a patient in the tranexamic acid group. (C, D) The course of recovery of a patient in the Kligman group (evaluation sessions in order from left to right)

TABLE 4 Frequency of pain, irritation, pruritus, bruising, and scaling in the two groups

Parameters	Items	Tranexamic acid	Kligman combination drug	*p*
Pain	Yes	12	9	0.287
	No	9	13	
	Total	21	22	
Irritation	Yes	13	16	0.339
	No	8	6	
	Total	21	22	
Bruising	Yes	0	0	-
	No	21	22	
	Total	21	22	
Pruritus	Yes	11	16	0.68
	No	10	6	
	Total	21	22	
Scaling	Yes	2	17	0.00
	No	19	5	
	Total	21	22	

demonstrated a significant reduction in hyperpigmentation of the skin in the treated areas.

4 | DISCUSSION

Studies have shown that the signs of skin aging are improved with the use of tranexamic acid. In addition, tranexamic acid inhibits the degradation of extracellular matrix (ECM), increases epidermal cell count, and artificially enhances skin hyaluronic acid by inhibiting plasmin and suppressing matrix metalloproteinase (MMP).[9] Despite the brightening properties of tranexamic acid, the effect of this compound in the treatment of MA has not yet been investigated, and therefore the present study evaluated the effectiveness of this drug in improving MA lesions.

The present study showed that both treatments were effective in improving MA and significantly reduced the hyperpigmentation in the treated areas, but the intralesional injection of tranexamic acid was significantly more effective than the topical application of the Kligman combination drug. The effects of tranexamic acid on melasma in reducing melanin have been well established.[15,16,18] A similar study in 2020 examined the role of oral tranexamic acid alone and in combination with hydroquinone in melasma patients; based on the results, the combination therapy with oral tranexamic acid and 4% hydroquinone cream was more effective for the treatment of melasma, in comparison with hydroquinone cream alone.[16]

In the present study, based on the opinion of the physicians, it was demonstrated that the rate of recovery of MA was significantly higher in the tranexamic acid group. In addition, the frequency of pruritus was lower in patients treated with tranexamic acid than in patients who were treated with the Kligman combination drug. In 2020, Menon et al. conducted a study and compared the usefulness and safety of microneedling in combination with topical tranexamic acid and microneedling in combination with topical vitamin C in the treatment of melasma. Their findings showed that the rate of recovery in patients treated with tranexamic acid was higher compared to those who were treated with vitamin C, although these differences were not significant.[17]

In our study, the efficacy of intralesional injection of tranexamic acid was investigated. A similar study has shown that intralesional injection of tranexamic acid is an effective treatment for melasma.[15] In 2019, Khurana et al. compared the effectiveness of oral and injectable tranexamic acid in melasma and reported that the effectiveness of oral tranexamic acid was higher compared to the injected form.[18] Also, Saleh et al. considered the intralesional injection of tranexamic acid to be effective in reducing brown spots on the skin.[19] Another study compared the effect of oral tranexamic acid and microinjection of this drug in melasma patients and proved the usefulness of tranexamic acid injection in reducing the hyperpigmentation of the skin caused by melasma disease.[20]

Tranexamic acid has been shown to be more effective than some routine medications in reducing hyperpigmentation caused by melasma. In 2019, Janney et al. showed that the therapeutic efficacy of tranexamic acid 5% solution was higher than hydroquinone cream in the treatment of melasma.[21] Another study on melasma showed that the combination of oral and topical tranexamic acid 3% was significantly more effective than the combination of oral tranexamic acid and 20% azelaic acid in the treatment of brown spots.[22]

In the present study, different follow-up periods were considered, and the patients who were treated for 3 months showed better improvement. In 2017, Saki et al. showed that in the first 4 weeks, the recovery was greater in the tranexamic acid group, but after 20 weeks, the overall changes were the same in both groups.[11] However, some studies have shown different results regarding the effectiveness of tranexamic acid. Elfar et al. demonstrated that the best therapeutic efficacy on melasma was observed in the group of

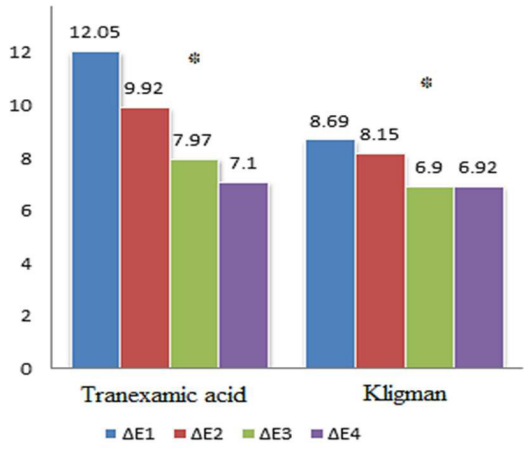

FIGURE 2 The difference in hyperpigmentation between the two study groups

TABLE 5 The separate evaluation of the effect of treatment on the study groups

Group			95% Confidence		p
			Lower	Upper	
Tranexamic acid	Pair 1	ΔE1 − ΔE2	1.18165	3.06692	0.000
	Pair 2	ΔE2 − ΔE3	0.87181	3.03486	0.001
	Pair 3	ΔE3 − ΔE4	−0.13151	1.87818	0.085
Kligman combination drug	Pair 1	ΔE1 − ΔE2	−0.09421	1.17785	0.091
	Pair 2	ΔE2 − ΔE3	0.65651	1.85713	0.000
	Pair 3	ΔE3 − ΔE4	−1.54728	1.49365	0.971

patients treated with glycolic acid and topical Silymarin, respectively, and tranexamic acid was significantly less effective.[23]

Studies have shown that tranexamic acid reduces hyperpigmentation by affecting the structure of the epidermis. Hyaluronic acid synthesis occurs more frequently in women due to female hormones, and the effect of tranexamic acid injection is stronger in females.[10] Kim et al. reported that tranexamic acid significantly reduced the severity of melasma in patients. Also, the side effects of this drug were very low and rarely included hypomenorrhea and gastrointestinal disorders.[24] In a similar study, Atefi et al. reported that no side effects were observed in the group of patients treated with tranexamic acid, but in the hydroquinone group, 10% of patients had local irritation and redness. They stated that tranexamic acid, with its low side effects and higher patient satisfaction is an appropriate medication for treating melasma and reducing hyperpigmentation.[25]

The authors of this study have been working on the etiologies and treatments of many hyperpigmented skin disorders,[26–32] and now it seems that there is not any long-lasting, safe, and highly effective therapy for macular amyloidosis, which we focused on in this RCT.

In relation to the findings of the present study, it can be stated that the therapeutic efficacy of the tranexamic acid and Kligman formula on MA is probably due to the effect of these drugs on the hormonal functions affecting melanocyte cells. Formerly, it has been hypothesized that TA can inhibit the release of paracrine melanogenic factors that normally act to stimulate melanocytes.[33,34]

Various studies have shown the association of melanin synthesis in specific organs called melanosomes with amyloid filaments. In fact, changes in the structure of melanosomes containing amyloid melanocytes have a direct effect on the deposition of amyloid filaments, and medications that inhibit and destroy melanocytes containing hydroquinone affect MA by reducing melanin content and deposition of amyloid filaments.[35,36]

However, in the present discussion, due to the novelty of the purpose of the study and the lack of studies related to MA (and knowing the fact that MA and melasma are completely different clinical entities), we also focused on the etiological association of melasma with MA in melasma-related therapies.

In general, the findings of our study demonstrate the role of intralesional injection of tranexamic acid in reducing hyperpigmentation and improving macular amyloidosis, so that along with the Kligman combination drug, it can be an appropriate treatment for these patients. In addition, these findings are consistent with similar studies on the effect of tranexamic acid on melasma.

One of the limitations of the present study was the lack of cooperation of some patients to continue the research and follow-up, which was solved by providing scientific explanations and knowledge of aspects of the research for them.

Since this study is a novel, there is no similar work on the treatment of MA with TA in the literature. This study has good results regarding the treatment of MA-which is one of hyperpigmentation skin disorders resistant to treatment-with TA and topical brighteners that can be very promising. However, studies related to the effectiveness of TA in skin hyperpigmentation disorders are mainly related to melasma, in the discussion we inevitably discussed the closest evidence and results, that is, evidence of melasma as rationale.

5 | CONCLUSION

The results of this study demonstrated the significant positive effects of both treatment methods, but in terms of reducing melanin content, intralesional injection of tranexamic acid was a more effective method. Both treatments considered safe for MA. In tranexamic acid group, patients logically experienced a tolerable pain during injection but they significantly had significantly lower local pruritic discomfort during study. So, based on the positive findings of this study we suggest to use tranexamic acid in combination with other effective therapeutic methods for treatment of MA especially use of its topically applied form in combination with non-aggressive needling that results in better drug delivery without the experience of injection pain. Selection of the best administration route of tranexamic acid for hyperpigmented lesions depends on the each patient characteristic and their previous theraputic results that may vary case by case. However, further studies with larger sample sizes in different populations are needed to better demonstrate the therapeutic efficacy of tranexamic acid. It is recommended that tranexamic acid be used as an adjunct to other treatments. Also, the follow-up period of the present study was short and further longitudinal studies in this regard are recommended.

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CONFLICT OF INTEREST

All the authors declare that there is no conflict of interest for this project.

AUTHOR CONTRIBUTIONS

Mohammadreza Ghassemi and Masoumeh Roohaninasab designed the study; Afsaneh Sadeghzadeh-Bazargan, Azadeh Goodarzi searched the literature and wrote the paper; Seyed Abolfazl Kamani, Afsaneh Sadeghzadeh-Bazargan, and Azadeh Goodarzi involved with acquisition of data; Seyed Abolfazl Kamani and Afsaneh Sadeghzadeh-Bazargan involved with analysis and interpretation of the data; all authors contributed in revising the paper critically for important intellectual content; all authors have read and approved the final manuscript.

ETHICS STATEMENT

The study was approved by the Ethics Committee of Iran University of Medical Sciences, code: IR.IUMS.FMD.REC.1398.138. The author obtained written consent for publishing the paper and accompanies images from the patient.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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