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CITATION:

Morimoto, Naoki ...[et al]. Cultured epithelial autografts for the treatment of large-to-giant congenital melanocytic nevus in 31 patients. Regenerative Therapy 2021, 18: 217-222

ISSUE DATE:

2021-12

URL:

http://hdl.handle.net/2433/277435

Regenerative Therapy 18 (2021) 217–222

Contents lists available at ScienceDirect

Regenerative Therapy

journal homepage: http://www.elsevier.com/locate/reth

Original Article

Cultured epithelial autografts for the treatment of large-to-giant congenital melanocytic nevus in 31 patients☆

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ARTICLE INFO

Article history:
Received 4 June 2021
Accepted 1 July 2021

Keywords:
Giant congenital melanocytic nevus
Curettage
Cultured epithelial autograft
L*a*b* color space

ABSTRACT

Introduction: Giant congenital melanocytic nevus (GCMN) is a large melanocytic nevus, and its full-thickness removal is usually difficult due to the lack of skin available for reconstruction. Curettage is an alternative approach in cases of GCMN to remove the superficial dermis above the cleavage plane with a curette in the neonatal period, and its major complications include repigmentation, retarded epithelization, and hypertrophic scar formation. In Japan, the JACE® cultured epidermal autograft (CEA) was approved and covered by public healthcare insurance for the treatment of congenital melanocytic nevus (CMN) that is difficult to treat with conventional methods in 2016. We have used CEA for wounds after curettage in the neonatal period or following ablation after the neonatal period in combination with laser therapies to reduce the above-mentioned complications.

Methods: In this study, we summarized all consecutive CMN patients treated using CEA from December 2016 to April 2019 and evaluated the duration required for epithelialization, incidence of hypertrophic scar, and color change in the target nevus by comparing the L* values one year later between the Curettage group, the non-Curettage group with initial treatment or the subsequent group.

Results: No significant differences were seen in the epithelization period or incidence of hypertrophic scars among the groups, but the color of the target nevus was improved significantly in the Curettage group ($p < 0.01$) and non-Curettage group with initial treatment ($p < 0.01$).

Conclusions: In conclusion, CEA seems to accelerate epithelization after curettage or ablation of CMN, and this treatment could improve the color of CMN when applied initially.

1. Introduction

Giant congenital melanocytic nevus (GCMN) is a large melanocytic nevus present at birth. It is defined as a nevus of >20 cm in diameter in adults and ≥9 cm on the head of neonates or ≥6 cm on the body [1,2]. In addition, several other definitions of GCMN have been reported, such as the new classification system based on the size and number of satellite nevi [3]. Genetic abnormalities of large-to-giant CMN have been analyzed [4,5], and newly developed molecular-targeted drugs, such as MEK inhibitors, have been reported [6]. An important issue to note with GCMN is the risk of malignant transformation, the incidence of which is reported to be 0.7%–8.2% [2, 7, 8]; however, despite this risk, the full-thickness removal of GCMN is usually difficult due to a lack of skin for reconstruction, and the ideal medical treatment has not yet been established [5,9].

Curettage was first proposed by Moss and involves removing the superficial part of the dermis above the cleavage plane with a curette [10]. A large number of melanocytic cells can be removed by this technique, and the nevus color is improved [11]. However, the potential to reduce the risk of melanoma with curettage remains

☆ This work has not been published elsewhere or presented at any conferences.

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Peer review under responsibility of the Japanese Society for Regenerative Medicine.

https://doi.org/10.1016/j.reth.2021.07.001

controversial, and the indicated age and nevus size are also being discussed [11–15]. The major complications after curettage have been reported to be repigmentation, retarded epithelization, itching, vulnerable skin, and hypertrophic scar formation [11,13].

In Japan, cultured epidermal autograft (CEA; JACE®; Japan Tissue Engineering Co., Ltd., Gamagori, Japan), which is prepared using Green's technique and have been used to treat severe burn patients around the world, were approved and covered by public health insurance for the treatment of large-to-giant CMN in 2016 [16,17]. Since then, we have applied CEA proactively for the treatment of CMN, especially after curettage and partial-thickness removal of CMN.

In this study, we retrospectively evaluated the outcomes and complications of CMN treatments with CEA and discussed the indications of curettage and alternative treatments when curettage cannot be performed.

2. Patients and methods

2.1. Ethics

This protocol received Institutional Review Board approval from Kansai Medical University Hospital (Approval No. 2020280).

2.2. Patients

In this study, we summarized all consecutive CMN patients treated using the CEA (JACE®; Japan Tissue Engineering Co., Ltd.) in Kansai Medical University Hospital by a single operator from December 2016 to April 2019. The indication of CEA covered by public health insurance in Japan is for the treatment of CMN that is difficult to treat with conventional methods. Therefore, we applied JACE® for CMN that could not be removed primarily covering >0.1% of the total body surface area (TBSA) on the face or >1% of the TBSA in other regions.

2.3. Operative procedures

A section of each patient's skin approximately 1 × 2 cm in size was taken from the groin region under local anesthesia for the preparation of CEA and sent to Japan Tissue Engineering Co., Ltd. The skin defect was sutured primarily. Cultivation usually takes three weeks.

For the operative procedure, we initially attempted curettage as described by Moss. When we were able to perform curettage in an area above the cleavage plane, we completed curettage using either a curette, surgical cutting bar (TPS system; Stryker, Kalamazoo, MI, USA), electric dermatome (Keisei Medical Industrial. Co., Ltd., Tokyo, Japan), the Hydrosurgery System (VERSAJET II system; Smith and Nephew Medical Ltd., Hull, UK), or a CO_2 laser (UAL3000DP, Medical U&A, Inc., Osaka Japan). These patients were assigned to the Curettage group. When we were unable to perform curettage in any area, we abraded the CMN using one of the above instruments until the black or brown color of the CMN had been eliminated macroscopically. These patients were assigned to the non-Curettage group; we also confirmed whether this procedure was the initial treatment or a subsequent treatment after previous treatments, such as curettage or Q-switched ruby laser irradiation. An epilation laser (GentleLase Pro; Candela Corporation, MA, USA) was used for hairy nevi, and a Q-switched ruby laser (Compact Laser 30C; Lumenis Japan Ltd., Tokyo, Japan) was used when the nevus color remained macroscopically.

We grafted CEA onto the raw surface, and CEA was fixed using silicone-faced dressing (SI-Mesh®; ALCARE Co., Ltd., Tokyo, Japan) as a contact layer and tie-over dressing. The tie-over dressing was removed around one week after grafting. The remaining wound was then covered using silicone wound dressing until epithelialization had been achieved. When hypertrophic scars were observed, pressure garments or silastic gel compression (Cica-Care; Smith and Nephew Medical Ltd.) was used.

2.4. Treatment assessments

Patients were followed up by a single operator after discharge, and the period until epithelialization occurred was observed. Digital photos of the target nevus were taken with a calibrator (ColorChecker Passport®; X-lite Inc., Grand Rapids, MI, USA) before the removal and at one year after each operation. The operator and another surgery specialist determined the Vancouver Scar Scale (VSS) score [18] at one year after the photos were taken, and patients with a VSS score >3 were judged to have hypertrophic scars. The VSS score was determined based on four parameters: vascularity (0–3), pigmentation (0–2), pliability (0–5), and scar height (0–3). The scar characteristics were rated from 0 (normal) to 13 (hypertrophic).

The Commission Internationale de l'Eclairage (CIE) L*a*b* was used to evaluate the change in color after treatment [19]. Digital photos of the target nevus were taken with a calibrator (ColorChecker Passport®; X-lite Inc.) before the removal and at one year after each operation. Photographs were calibrated using the Adobe Photoshop Lightroom classic software program (Adobe Inc., San Jose, CA, USA) with plugins supplied by X-lite Inc. Images were analyzed using the Adobe Photoshop CC software program (Adobe Inc.), and L*a*b* values were evaluated. The L* value represents the darkest black at L* = 0 and the brightest white at L* = 100, so the L* values of the nevus before its removal and at one year after each operation were compared.

2.5. Statistical analyses

L* values were expressed as the mean ± standard deviation (SD). Statistical differences of epithelization days and L* values between groups were analyzed using an analysis of variance (ANOVA) and the Tukey–Kramer test. Statistical differences in the incidence of the hypertrophic scars between groups were analyzed using Mann–Whitney's U test. P values of <0.05 were considered to indicate statistical significance. The Microsoft Excel software program (Microsoft Corp. Redmond, WA, USA) with the Statcel 3 software add-in (Oms publishing Inc., Tokyo, Japan) was used for the statistical analyses.

3. Results

3.1. Patients

The demographics of the 31 patients and localization of CMN are shown in Table 1. Two patients had 2 lesions, and 1 patient had 3 lesions treated using CEA in different regions, so 35 lesions were

Table 1
Patient demographics and localization of CMN.

Total number of patients	31
Total number of treated CMN	35
Mean age at the first operation, mean (range)	2.6 y (3 m-15 y)
Sex, male:female	12:19
TBSA (%), mean (range)	7.3 (0.1–60)
Localization (%)	
Trunk	6 (19.3)
Head and neck	24 (67.7)
Upper extremities	4 (12.9)
Lower extremities	1 (0.03)

Two patients had 2 lesions and one patient had 3 lesions in different regions.

ultimately included. The mean age at the first operation was 2.6 years old (range, 3 months-15 years old), and 24 lesions (67.7%) were located in the head and neck. The mean area of the DMN was 7.3% (range, 0.1%–60%) of the TBSA.

Regarding the practice of curettage, 38 initial surgeries for CMN of 25 patients were performed. Curettage was able to be performed in 29 lesions of 17 patients, while it could not be performed in 9 lesions of 8 patients (Table 2). In the Curettage group, 1 patient had undergone 4 surgeries, 2 patients had undergone 3 surgeries, and 5 patients had undergone 2 surgeries according to the size of CMN, so 29 initial surgeries for CMN were included. Ablation using a CO_2 laser (27 lesions), electric dermatome (3 lesions), or hydrosurgery system (2 lesions) was added to remove the superficial layer of the remaining nevus in patients in the Curettage group. When curettage could not be performed using a curette, ablation using a CO_2 laser (9 lesions), electric dermatome (2 lesions), or cutting bar (1 lesion) was performed in the non-Curettage group with initial treatment. In the non-Curettage group with subsequent treatment, CMN had previously been treated by curettage (3 lesions), ablation with a cutting bar (2 lesions) or CO_2 laser (3 lesions), multiple sessions of irradiation with a ruby laser (2 lesions), or cryotherapy (1 lesion). CMNs were abraded using a CO_2 laser (11 lesions) or cutting bar (6 lesions) and irradiated with a ruby laser (6 lesions) when the nevus color remained. An epilation laser was used to treat hairy CMN in all groups. After these treatments, CEA was applied to the nevus.

3.2. Results of treatment assessments

The mean period of epithelization was 28.9 days (range, 9–120) in the Curettage group, 34.6 days (range, 12–90) in the non-Curettage group with initial treatment, and 13.6 days (range, 9–19) in the non-Curettage group with subsequent treatment. Hypertrophic scar formation was observed in 10 (35.7%) lesions in the Curettage group, 2 lesions (22.2%) in the non-Curettage group with initial treatment, and 1 lesion (9.0%) in the non-Curettage group with subsequent treatment. Significant differences were not seen in the epithelization period or incidence of hypertrophic scars among the groups.

Regarding improvement in the color of the target nevus, the L* increased significantly in the Curettage group ($p < 0.01$) and non-Curettage group with initial treatment ($p < 0.01$), whereas no significant difference was observed in the L* before and after ablation the non-Curettage group with subsequent treatment.

3.3. Case presentation

- Case 1 (Curettage group)

A 5-month-old girl had a large hairy GCMN at her left forehead and upper eyelid (Fig. 2A). A skin specimen 1 cm^2 in size was taken from her groin region to prepare JACE® at 4 months old. We performed curettage of the whole GCMN and abraded the remaining nevus using a CO_2 laser, and irradiated the CMN with the epilation laser. We then applied JACE® to the whole wound (Fig. 2B). The wound had mostly been epithelialized by two weeks after surgery (Fig. 2C), but recurrence of the erosion was observed at three weeks (Fig. 2D). We applied silicone-faced wound dressing, and the erosion slowed and ultimately epithelized at 120 days after surgery. At one year later, the nevus color was improved, and a hypertrophic scar (VSS score 3) was observed at the internal side of the left

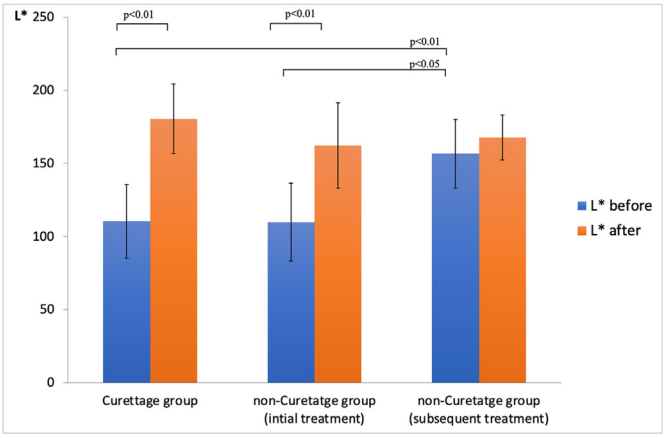

Fig. 1. The comparison of the L* values before and after each treatment. The L* value increased significantly in the Curettage group ($p < 0.01$) and in the non-Curettage group with initial treatment ($p < 0.01$). The L* values before treatment in the non-Curettage group with subsequent treatment were significantly larger than those before treatment in the Curettage group ($p < 0.01$) and the non-Curettage group with initial treatment ($p < 0.05$).

Table 2
Patient Demographics and treatment results.

Excision procedure	Curettage group	non-Curettage group (initial treatment)	non-Curettage group (subsequent treatment)
Total number of patients	17	8	9
Total number of operations	29	9	11
Mean age at the curettage peration (range)	0.83 y (3 m-4y)	4.1 y (3 m-15 y)	5.1 y (1 y-15 y)
TBSA (%), mean (range)	6.1 (2–20)	17.6 (0.2–60)	2.0 (0.1–8)
Treated area in single operation (BSA%), mean (range)	3.4 (1–5)	2.1 (0.1–5)	1.22 (0.1–3)
Localization (%)			
Trunk	10 (35.7)	4 (44.4)	9 (81.8)
Head and neck	17 (60.1)	5 (55.5)	2 (18.1)
Upper extremities	2 (7.1)	0 (0)	0 (0)
Lower extremities	0 (0)	0 (0)	0 (0)
Combined treatment with curettage			
Dermatome	3 (10.7)	2 (22.2)	0 (0)
Hydrosurgery system	2 (7.1)	0 (0)	0 (0)
Cutting bar	0 (0)	1 (11.1)	6 (54.5)
CO2 laser	27 (96.4)	9 (100)	11 (100)
Epilation Laser	15 (53.6)	1 (11.1)	6 (54.5)
Ruby Laser	0 (0)	0 (0)	6 (54.5)
Treatment results			
Epithelization (days), mean (range)	28.9 (9–120)	34.6 (12–90)	13.6 (9–19)
hypertrophic scar at one yearafter operation (%)	10 (35.7)	2 (22.2)	1 (9.0)

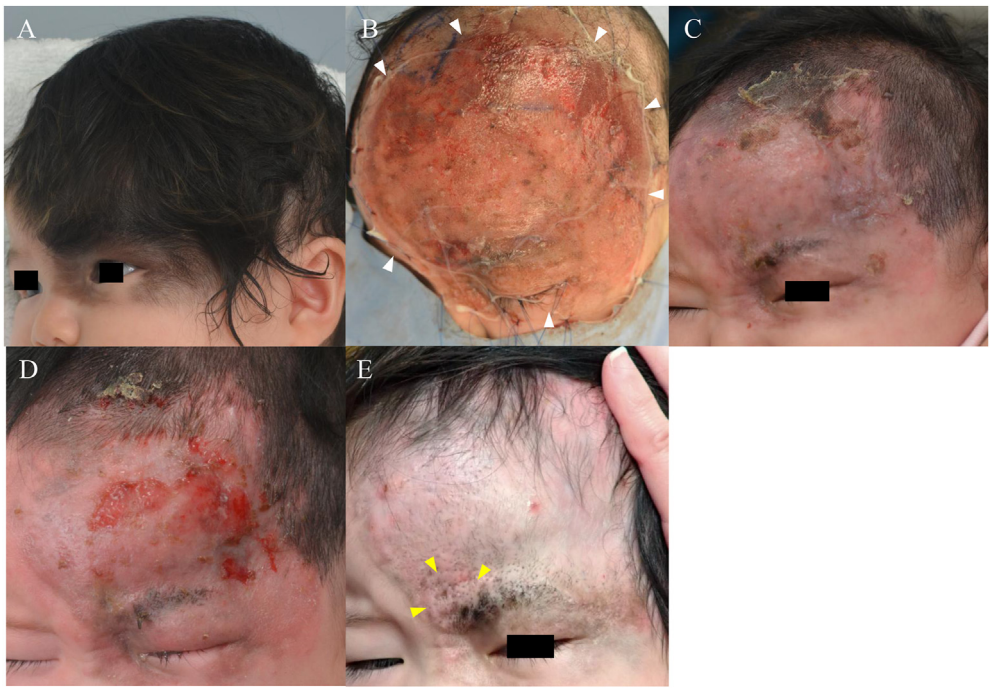

Fig. 2. The time course of Case 1 in the Curettage group. A: GCMN before curettage. B: GCMN after curettage and the application of JACE®. The white arrowheads indicate the margin of JACE®. C: The gross appearance at two weeks after surgery. D: The erosion relapsed at three weeks. E: The gross appearance at one year. The yellow arrowheads indicate the hypertrophic scar.

eyebrow (Fig. 2E). The L* values before and after were 146.5 and 217.4, respectively.

- Case 2 (non-Curettage group with initial treatment)

A 4-year-old girl had a CMN on her right cheek (Fig. 3A). After preparing JACE®, the CMN was abraded using a CO_2 laser, and the JACE® was grafted (Fig. 3B). We then applied the JACE® to the whole wound (Fig. 3B). The wound seemed to be epithelialized at two weeks after surgery (Fig. 3C). Although the erosion relapsed (Fig. 3D), the wound was ultimately epithelized at 90 days. At one year later, small recurrence of the nevus was observed in the hypertrophic scar (VSS score 4) (Fig. 3E). The L* values before and after were 79.4 and 173.4, respectively.

- Case 3 (non-Curettage group with subsequent treatment)

A 15-year-old boy had a GCMN on his right forehead, upper and lower eyelid, and the dorsum of his nose (Fig. 4A). He had received ruby laser irradiation over 10 times. After preparing a JACE®, the GCMN was abraded using a surgical cutting bar, and the JACE® was grafted. The wound had epithelialized by three weeks after surgery (Fig. 4B). At one year later, hypertrophic scars (VSS score 4) were observed around the dorsum of his nose (Fig. 4C). The L* values before and after were 146.7 and 179.1, respectively.

4. Discussion

In this study, we initially attempted curettage of CMN using a curette for 31 patients and performed ablation of the CMN with a cutting bar, electric dermatome, hydrosurgery system, and/or CO_2 laser when curettage could not be performed.

Regarding the possibility of performing curettage, Moss stated that curettage should be performed before six months of age but preferably as early as possible, as nevus cells migrate deeper into the dermis from the upper layers with age [10]. Rasmusen et al. recently performed curettage of 16 patients with a mean age of 27 days (range, 10–66 days) [11], and Gatibelza et al. reported 20 CMN patients who received curettage for CMN with a mean age of 13.7 days (range, 5–30 days) [12]; in addition, curettage has been performed until 10 weeks of age in many reports [14]. Regarding the possibility of performing curettage after 10 weeks old, Whang et al. treated a one-year-old CMN patient with curettage and ablation using an erbium YAG laser, and abraded CMN using an erbium YAG laser for patients over three years old [13]. In addition, Kishi et al. treated 23 CMN patients from 1 month to 19 years old with curettage and performed additional dermablation using a CO_2 laser or grinder, confirming the cleavage plane in all patients [15].

In this study, the mean age of the Curettage group was 0.83 years old (range, 3 months-4 years old), and that in the non-Curettage group with initial treatment was 4.1 years old (range, 9 months-15 years old). As for the practice of curettage, curettage was able to be easily performed at the central area of the CMN but was usually difficult to perform at the edge of the CMN; therefore, a CO_2 laser was used to abrade such difficult-to-manage areas in 96.4% of patients in the Curettage group. The area where curettage could be performed easily gradually shrank with age, and curettage of only a small area of the CMN could be performed in a 4-year-old patient in the Curettage group. Given these results, curettage seems feasible until around one year old, but its practice becomes difficult with age for the initial treatment of CMN.

Regarding the effectiveness of curettage, we evaluated the change in color after curettage based on the L* value, which represents the absolute value of darkest black. The L* value at one year later in the Curettage group had improved significantly ($p < 0.01$, Fig. 1), suggesting that the pigmentation of the CMN can be improved by curettage. When curettage could not be conducted, we abraded the superficial layer of the CMN using one of the above-mentioned methods until the color had been eliminated macroscopically. Regarding the effectiveness of ablation, the L* values of

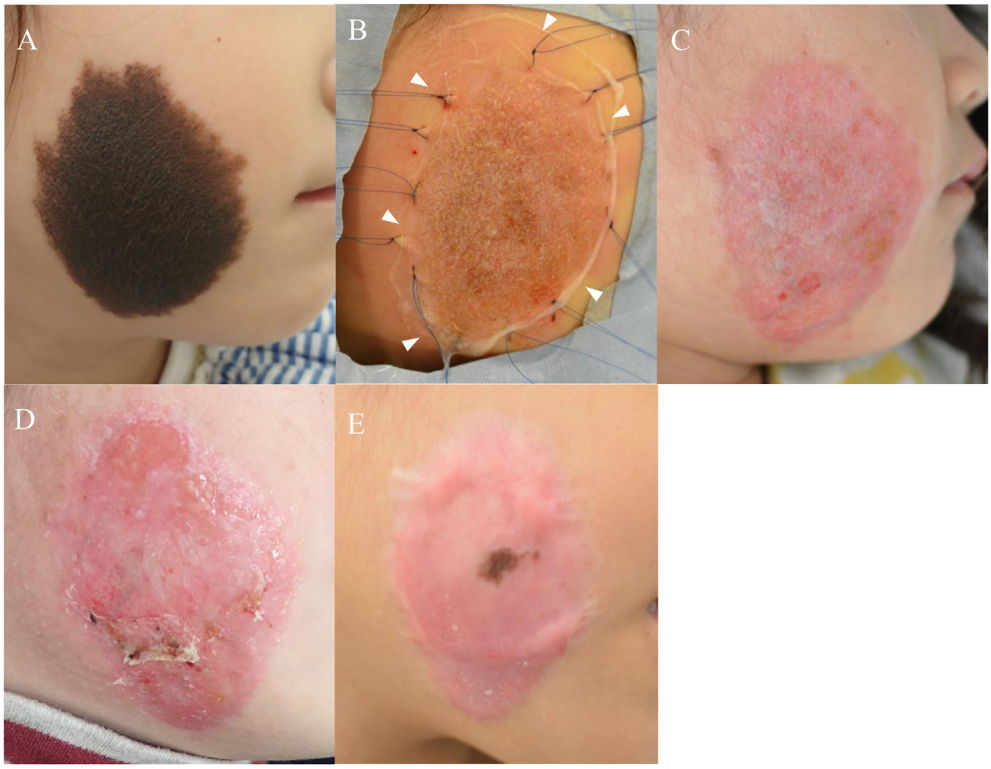

Fig. 3. The time course of Case 2 in the non-Curettage group with initial treatment. A: CMN before curettage. B: CMN after ablation and the application of JACE®. The white arrowheads indicate the margin of JACE®. C: The gross appearance at two weeks after surgery. D: The erosion was still observed at 60 days after surgery. E: The gross appearance at one year.

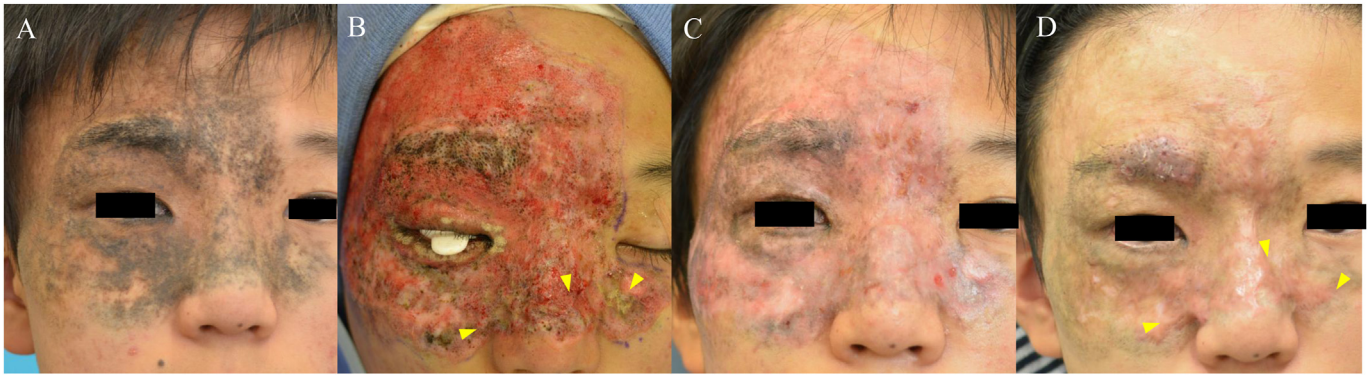

Fig. 4. The time course of Case 3 in the non-Curettage group with subsequent treatment. A: GCMN before curettage. B: GCMN after ablation using cutting bars. The yellow arrowheads indicate the nevus that was deeply ablated to remove pigmentation. C: The gross appearance at three weeks after surgery. D: The gross appearance at one year. The yellow arrowheads indicate the hypertrophic scar.

the non-Curettage group with initial treatment were also improved significantly ($p < 0.01$, Fig. 1), whereas the L* values of the non-Curettage group with subsequent treatment were not significantly improved after treatment. The L* value before treatment in the non-Curettage group with subsequent treatment was greater than that in the Curettage group and non-Curettage group with initial treatment, probably because the color of the target nevus was improved to some extent by the previous treatments, including curettage, ablation, and laser therapies.

Regarding the effectiveness of CEA, Whang et al. reported that CEA shortened the complete healing time, with a mean value of 37.0 days (range 14–84 days) in the CEA group versus 76.3 days (range 26–150 days) in the non-CEA group after curettage or ablation with an erbium YAG laser for CMN [13]. In this study, the mean period of epithelization was 28.9 days (range, 9–120 days) in the Curettage group, 34.6 days (range, 12–90 days) in the non-Curettage group with initial treatment, and 13.6 days (range, 9–19 days) in the non-Curettage group with subsequent treatment. We used CEA in all cases, and our epithelization periods seem compatible with those of Whang et al., suggesting that CEA can accelerate epithelization after curettage or ablation of CMN. However, we must be alert for cases in which erosion healing is delayed, which can occur when erosion persists for several weeks or relapses soon after epithelization, as in cases 1 and 2.

Concerning the hypertrophic scar formation, we were unable to evaluate the effect of CEA, but the wounds with delayed healing, such as in cases 1 and 2, or with deep ablation to remove the CMN, such as in case 3, showed hypertrophic scars. This indicates that CEA cannot always prevent hypertrophic scar formation. In the non-Curettage group with subsequent treatment, we performed irradiation with an epilation or ruby laser in 54.5% of cases to remove the remaining color after ablation. The CEA survived successfully in these cases, suggesting that it may be a viable alternative after combination treatment with curettage or ablation and laser therapies.

One limitation of this study is that we did not evaluate the effectiveness of curettage or ablation in association with the histopathology of CMN. We collected histological samples from all patients, but we were only able to obtain the superficial nevus removed by curettage in some cases of the Curettage group. In addition, we observed rapid severe repigmentation within six months in one patient each in the Curettage group and the non-Curettage group with initial treatment. As our next step, we will evaluate the association of the histology with recurrence or repigmentation.

In conclusion, CEA seems to accelerate epithelization after curettage or ablation in combination with additional laser therapies. Such combination therapy could improve the pigmentation of CMN when the treatment is an initial one.

Funding

The authors received no funding for the preparation of this manuscript.

Declaration of competing interest

The authors (NM, KY, SO, IT and MS) were financially supported by Japan Tissue Engineering Co., Ltd (J-TEC) for their collaborating research at Kyoto University. However, all operations of this manuscript were carried out at Kansai Medical University Hospital and the company did not have any role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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