







Selected treatment methods for colloid milium – a literature review

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ABSTRACT

Introduction and aim. Colloid milium is a rare degenerative skin condition of unknown origin. Typically, it affects sun-exposed areas of the skin. Nevertheless, non-sun-exposed areas may also be affected. Clinically it presents with yellow or red papules, filled with gelatinous masses. There are four subtypes of colloid milium, each with its distinct characteristics: adult, juvenile, nodular, and pigmented. Although diagnosis is primarily clinical, skin biopsy and various staining techniques are required to exclude similar diseases. There is no single effective treatment for colloid milium. Most methods involve the use of lasers, dermabrasion, and oral medications. Yet, the final results differ.

Since this topic has not been addressed very frequently in recent literature, the purpose of this review is to present the currently available treatment methods for colloid milium.

Material and methods. A literature review was performed to identify the most efficient treatment approaches for colloid milium, focusing on their effectiveness in eliminating nodules and preventing recurrence.

Analysis of the literature. Due to its rarity and consequent lack of extensive scientific research, the number of available therapy options for colloid milium is limited. Commonly used treatment methods include lasers, oral medications, dermabrasion, and photodynamic therapy. Microablative fractionated CO₂ laser treatment resulted in complete ablation of the lesions with no recurrence. Non-ablative fractional resurfacing after multiple therapies led to the total elimination of the lesions, with no signs of reappearance during follow-up. Dermabrasion required a lengthy healing process. During follow-up no new papules were detected. After multiple sessions of treatment with MAL-PDT, the skin was devoid of nodules and recurrence was prevented. Following full recovery, treatment with the long-pulsed ER:YAG laser revealed the skin without any textural changes, scars, or pigmentation. During follow-up, no new papules were reported. Oral medication provided insignificant results. The majority of patients undergoing these procedures did not need preparation or analgesia. However, non-ablative fractional resurfacing required topical analgesia with 30% lidocaine gel, long pulsed Er:YAG laser treatment demanded intravenous sedation, and dermabrasion involved axillary block analgesia. None of the procedures provoked adverse effects.

Conclusion. Skin lesions caused by colloid milium may provoke esthetic concerns, prompting patients to remove them. However, available treatments methods are limited and yield varying outcomes. Among the prominent procedures are microablative fractionated CO₂ laser, non-ablative fractional resurfacing, long pulsed ER:YAG laser, and treatment with MAL-PDT, which led to complete ablation, required minimal convalescence time, and provided long-lasting remission. Dermabrasion displayed partial results, with no observed relapse of colloid milium during follow-up. Oral treatment presented the least significant results. Further research is necessary in order to develop new treatment methods for colloid milium that are safe, effective, and affordable.

Keywords. adult colloid milium, colloid milium, colloid milium treatment, juvenile colloid milium, juvenile colloid milium treatment

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Introduction

Colloid milium (CM), alternatively referred to as colloid degeneration of the skin or dermal hyalinosis, is a rare degenerative dermatological condition with an unknown origin.^{1,2} It is characterized by the deposition of colloid in the cutis, particularly in sun-exposed areas such as the face, neck, cheeks, dorsum of hands, forearms, back, nose, and ear.^{1,3,4} However, colloid milium may also affect the non-sun-exposed areas, such as the oral cavity, the inner part of the tragus, the eyelid margins, trunk and penis.⁵⁻¹⁰ Microscopic examination reveals homogenous and amorphous eosinophilic masses in the dermis.¹¹⁻¹³ Clinically, it presents with 0.5–5 mm amber, flesh-colored, or yellow papules and pseudo vesicles, from which a mucoid or gelatinous fluid can be expressed with gentle pressure or puncture.^{2,4,12,14,15} Any injury to the skin lesions may lead to the development of purpura.^{10,16} There are typically four subtypes of CM, each with distinct etiologies and origins: adult colloid milium (ACM), juvenile colloid milium (JCM), nodular, and pigmented.^{17,18} The ACM occurs between the ages of 30 and 50. It affects more males than females, with a ratio of 4:1, and is thought to be caused by the destruction of the elastic fibers.^{1,2} The JCM is associated with the degeneration of UV-transformed keratinocytes, which results in formation of deposits in the dermis and epidermis.^{4,19} The literature suggests that a juvenile subtype might be inherited (familial JCM) in an autosomal recessive or dominant pattern, and can present before puberty.²⁰⁻²² Chemicals and toxins such as petroleum and hydroquinone may contribute to the pigmented subtype of CM.^{23,24} The nodular subtype can be observed in older patients.¹⁸ Some authors recognize an additional subtype - acral keratosis with eosinophilic dermal deposits (AKEDD), which is extremely rare.¹³ In reports by Abalos-Babaran et al. from 2019 and Azzazi et al. from 2023, there is a correlation between CM and vitamin C deficiency, trichinosis, and beta-thalassemia. However, this connection remains controversial.^{25,26} Colloid milium may be confused with amyloidosis, sarcoidosis, Favre-Racouchot disease, trichoepitheliomas, syringomas, sebaceous hyperplasias, common milium, molluscum contagiosum, steatocystoma multiplex, papular mucinosis, lipid proteinosis, senile sebaceous hyperplasia, and retention cyst. Therefore, the key to diagnose dermal hyalinosis is to perform a full-thickness skin biopsy.^{11,15,17} Staining with crystal violet, hematoxylin and eosin (H&E), periodic acid-Schiff (PAS), and Congo red is crucial to make colloid masses visible.^{10,27} Figure 1 illustrates colloid depositions alongside solar elastosis within the cutis.²⁷ While, a patient's history is helpful in making a diagnosis.²⁸ Since adult colloid milium is infrequent, there is currently no effective treatment for it.^{9,29} Systemic ascorbic acid or exfoliative products have proven ineffective. Even topical retinoids

in combination resulted in insignificant cosmetic outcome.^{4,10} Case reports present various approaches to management of CM.²⁹ These methods incorporate the use of topical retinoids, creams containing urea, cryotherapy, chemical peels, oral medications, microablative fractionated CO₂ laser, non-ablative fractional resurfacing, dermabrasion, long-pulse Er: YAS laser treatment, and methyl aminolevulinate photodynamic therapy.^{29,30-32}

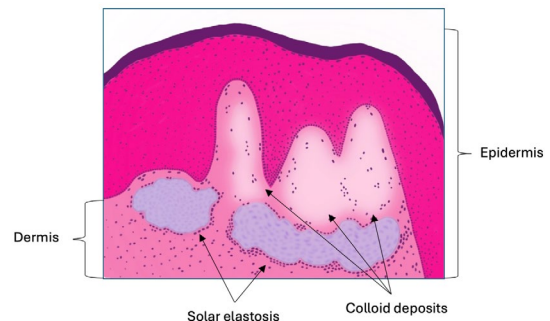


Fig. 1. Visualization of colloid milium within the skin tissue²⁷

Aim

The objective of this literature review is to present and evaluate the efficacy of contemporary treatment methods for colloid milium.

Material and methods

This review was conducted using electronic databases, including PubMed, Medline, Elsevier, and Google Scholar, to search for articles presenting treatment methods for colloid milium. We utilized the following keywords: “Colloid milium”, “Adult colloid milium”, “Juvenile colloid milium”, “Colloid milium treatment”, “Juvenile colloid milium treatment”. Articles were selected based on their relevance to the subject. The inclusion criteria consisted of literature reviews, case reports, and histochemical studies written in English. We excluded abstracts, duplicates, and irrelevant articles.

The initial exploration, applying the described keywords and criteria, yielded a total of 115 publications. Subsequently, duplicates and irrelevant publications were removed. Fig.2 demonstrates the inclusion and exclusion criteria used in this process. Afterward, 52 identified manuscripts underwent a thorough examination, resulting in the selection of 36 articles (31 case reports (9 depicting treatment methods, 22 with none or insufficient treatment description, yet displaying significant diagnostic value), 4 review articles, and 1 histochemical study) to be included in this literature review. The array of available therapy options for colloid milium is constrained by its rarity and the consequent lack of extensive scientific research. The described treatment approaches were chosen based on their accessibility as well

as their efficacy in both eliminating existing lesions and preventing recurrence.

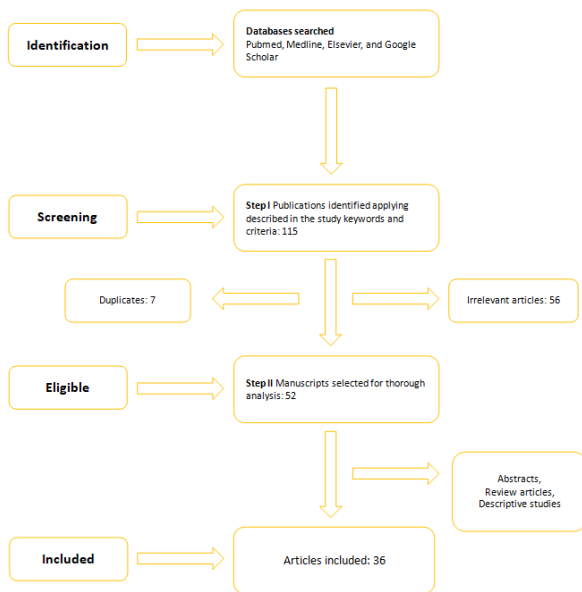


Fig. 2. A flow chart illustrating the process of literature research

Analysis of the literature

Based on the literature, in this review we are going to focus on the selected methods for treating colloid milium, including microablative fractionated CO₂ laser, non-ablative fractional resurfacing, long pulsed Er:YAG laser, oral treatment, dermabrasion, and photodynamic treatment with methylaminolevulinic acid (MAL-PDT). Table 1 illustrates the summary of presented treatment methods.^{5,25,29,31-36}

Microablative fractionated CO₂ laser

In a 2013 case report by Li et al. a 33-year-old male patient, presented with yellow papules measuring 1–5 mm in size on the forehead, jowl, nose, and lips. The patient experienced pruritus and discharge upon pressing the lesions. Histopathological examination revealed the presence of gelatinoids and horizontal fissuring enclosed by the solar elastosis. Cells with a hyaline composition within horizontal clefts and a wavy appearance distinguished it from amyloidosis. Following the diagnosis of CM, he received treatment with a microablative fractionated CO₂ laser (Lumens Ltd, Santa Clara, CA, USA) emitting at a wavelength of 10600 nm. The utilized parameters were: shape 3 (square), size 4, density 7, energy 125 mJ and frequency 200 Hz with pulse delay of 0.3 seconds. Along with laser treatment a test patch was performed on the patient's forehead. The whole procedure involved eight ablations until residual fluid emerged and was removed. The lesions were then cleared with gauze. After 4 days, the patient's forehead appeared smooth and devoid of lesions, with no

additional papules observed on the skin. During the 3-month follow-up, no new lesions were reported on the treated area, and no side effects were detected. Good cosmetic results were achieved.³²

In a 2019 case report by Abalos-Babaran et al. a 65 year old female patient, suffering from chronic kidney disease, presented with a 6 month history of yellow papules on her eyelids, periorificial area, concha of both ears, and in the oral cavity. Following punch biopsies of the lesions and revealing in the histopathologic examination depositions of amorphous, pale, homogeneous eosinophilic material; atrophic epidermis with a thin grenz zone; along with elastosis in the dermis and inflammatory infiltrate enclosing the eosinophilic deposits, the female was diagnosed with CM. Initially, the patient was prescribed a tretinoin cream with a concentration of 0.025% to be applied on her entire face at night. During the daytime, she was instructed to use sun protection with SPF 30. Subsequently, the patient underwent lesion ablation on her face using a microablative fractionated CO₂ laser, with a wavelength of 10600 nm. Two modes of this laser were employed: fractional active mode, size square, delivering energy of 300mJ, with a depth level of 5um for the periorbital area, which is layered with thinner skin and thus prone to purpura, and surgical mode for the perinasal and perioral areas. The results were assessed after two weeks. The periorbital area exhibited slight thinning of the plaques with complete re-epithelialization. A significant improvement was observed in the perinasal and perioral areas, where the skin lesions were completely ablated.²⁵

Non-ablative fractional resurfacing

In a 2007 case report by Marra et al. a 54-year-old male patient presented with yellow plaques and pseudovesicles on his cheek. Histopathology displayed eosinophilic hyalinized depositions in the papillary dermis, with positive Congo red staining. He was diagnosed with CM and underwent a series of fractional resurfacing treatments using a commercially available non-ablative 1550 nm diode-pumped erbium fiber laser (Fraxel, Reliant Technologies, Palo Alto, Calif). The device operates via photothermolysis, generating an array of extremely thin microscopic dermal zones, reaching depths ranging from 400 to 700 um and having a diameter of 100 um. This process induces a column of thermal damage, leading to collagen denaturation within the treated area. Before treatment, a tracking dye was applied, followed by a 30% lidocaine gel, which was left in place for about an hour. In total, 5 sessions were performed, with intervals of 2 to 3 weeks between each session. The laser parameters: fluence 20mJ, 125 microthermal zones per square centimeter, with 10 to 12 passes applied, delivering 1.6 to 2.1 kJ energy per session. Overall, the patient responded well to the therapy. However, there were no

remarkable changes after the first and second sessions. The changes began to occur after the third treatment. After the last (fifth) procedure, the patient's skin surface improved significantly, leaving it completely clear.³³

In a 2014 case report by Zeng et al. a 58-year-old female patient presented with asymptomatic yellow plaques on her face. Histopathological findings presented deposits of amorphous and fissured material in the sub-epidermis, as well as epidermal thinning. Congo red staining was negative. The patient was diagnosed with ACM and underwent treatment with a non-ablative 1550 nm wavelength erbium-glass fractional laser system (Sellas, Dinona Inc. Seoul, South Korea). The machine was set to a density of 100 MTZ/cm² along with a fluence of 80 mJ/cm². The affected area was covered with 4 to 5 passes during each session. A total of 5 sessions were performed to achieve the final results. The improvement in the skin condition was significant. After 6 months, there was no recurrence.²⁹

Long Pulsed Er:YAG Laser

In a 2002 case report by Ammirati et al. a resurfacing long-pulsed Er:YAG laser (CO₂) with a wavelength of 2940 nm that has a higher affinity to water than the CO₂ laser, is absorbed readily by collagen, and creates zones of thermal damage ranging from 40 to 60 µm, was used on a 41 year old male patient who presented with extensive 1–5 mm yellow papules on his forehead, nose, cheek, temples, chin, and lower lip. Histological examination revealed hyalinized depositions inside the papillary dermis and solar elastosis, leading to CM diagnosis. Before the procedure, a test area on the left temple was treated. Thereafter, the treatment area was locally anesthetized with 1% lidocaine plus epinephrine 1:100,000. The laser parameters used were: a dozen passes at 8.5 J/cm² with 4 msec pulse duration and a 5 mm spot size. These parameters resulted in the ablation of up to 80% of the affected skin areas. The procedure concluded with covering the treated area with Second Skin (Spenco Medical Co. Waco, TX) for 48 hours. Subsequently, the skin was washed three times a day with acetic acid compress (concentration 0.25%) followed by application of Aquaphor healing ointment (Beiersdorf, Wilton, CT). A patch test conducted earlier resulted in completely epithelialized skin after 10 days. No signs of scars, textural changes or pigmentation were seen. At the 6 month follow-up, there was no recurrence. Thus, the patient opted for another full face resurfacing, this time under deep intravenous sedation. Preparation for the operation involved the use of tretinoin cream with a concentration of 0.5% for 6 weeks. Additionally, on the day of surgery, he commenced oral dicloxacillin 250 mg twice a day for 7 days, valacyclovir 500 mg twice a day for 20 days, and prednisone 60 mg, tapering to 20 mg over 4 days. The same laser was utilized, with different param-

eters – a CO₂ laser at 9.8 J/cm² with a 5 mm spot and 10 msec pulse duration to increase the homeostasis. Initially, the entire facial skin was resurfaced with 50% overlapping passes. Then, the CO₂ laser was focused on the most affected areas, which led to ablation of 80% of the lesions with at least 10 passes. Moderate bleeding from deeper wounds was observed and managed by applying a gauze soaked in a combination of 1% lidocaine plus epinephrine 1:100,000 and aluminum chloride solution. Post operative wound care included applying Silon TSR (BioMed Sciences, Bethlehem, PA) for 3 days, followed by a compress of 0.25% acetic acid with Aquaphor healing ointment three times a day. Overall, the patient's recovery was smooth and uneventful. Complete epithelialization of the skin was achieved within 14 days. The patient was instructed to use sun protection regularly. At the 7 months follow-up examination, there were no signs of scarring, textural changes, or reappearance of CM. Moreover, a patch test performed on the left temple 13 months after the procedure showed no signs of hypopigmentation or recurrence.³⁴

Oral treatment

Instances of colloid milium in the oral cavity are very rare. There are only a few documented reports describing this condition. In a 2008 case report by Ojha et al. an 83-year-old male patient presented with 1-2 mm nodules in the oral cavity and concomitant papules on the left side of his face. The lesions manifested as nodule-shaped formations located submucosally, affecting his lower lip and the borders of the tongue. The lesions were tender to touch, giving him a painful sensation. Histopathological examination displayed amorphous eosinophilic deposits. Congo red staining was negative. PAS staining for eosinophilic material was positive. Following the diagnosis of CM, the man was prescribed a topical ointment for use within the oral cavity. The cream contained fluocinonide (Lindex) in a concentration of 0.05% with Orabase. Surgical procedures were also considered. However, the patient did not attend the next appointment. Consequently, the efficacy of this oral treatment remains unknown.⁵

In a 2019 case report by Voicu et al. a 10 year old boy presented with multiple 2-5 mm skin lesions on his nose, cheeks and upper lip. Histopathology revealed papillary findings with amorphous eosinophilic masses, along with thinning of the epidermis, and dilated capillary vessels. Congo red staining was negative. PAS staining was positive. The patient was diagnosed with JCM and treated with oral medications. He was recommended to apply sunscreen and take 250 mg of vitamin C daily. Upon reevaluation during the subsequent visit, there was slight improvement noted in his skin condition. Still, the changes were not significant. No new papules were observed during the follow-up examination.³¹

Table 1. Summary of described treatment methods^{*5,25,29,31-36}

Paper	Age/Gender	Location of lesions	Family history	Clinical presentation	Histological aspects	Size (cm)	Treatment method	Use of anesthesia	Time until effects appear	Outcome
Li et al.	33/M	Forehead, nose, lips, jowl	Negative	Yellow spots, pruritus, and discharge after pressing the lesions	Hyaline masses, upper dermis and dermal papilla layer composed of gelatinous fissure and solar elastosis	1–5 mm	Microablative fractionated CO ₂ laser	N/A	4 days	Complete ablation of lesions, no recurrence during a 3 month follow-up
Babaran et al.	65/F	Eyelids, periorbital area, concha of both ears, oral cavity	N/A	Multiple yellow papules and plaques, hemorrhage on the left periorbital plaque	In H&E staining, deposits of amorphous, homogenous, pale eosinophilic material, atrophic epidermis with a thin grenz zone, elastosis in the dermis and inflammatory infiltrate around the eosinophilic deposits	N/A	Microablative fractionated CO ₂ laser	N/A	2 weeks	Subtle thinning of the plaques with re-epithelialization on the periorbital area. In the perinasal and perioral areas complete ablation of lesions
Marra et al.	54/M	Cheeks	Negative	Large yellow plaques, pseudovesicular lesions	Biopsy exposed eosinophilic hyalinized deposits inside the papillary dermis, staining with Congo red was positive	N/A	Non-ablative fractional resurfacing	30% lidocaine gel	After the third session.	Completing 5 therapies left skin with no visible lesions
Zeng et al.	58/F	Face	Negative	Yellow colored papules	Thinning of the epidermis, amorphous and fissured material in sub-epidermis, staining with Congo red was negative	N/A	Non-ablative fractional resurfacing	No needed	After 5 treatments	6 months after the last procedure, the face was lesions-free without any new changes
Ammirati et al.	41/M	Forehead, temples, nose, lower lip, cheeks, chin	Negative	Solid amber colored papules	Punch biopsy exhibited hyalinized masses within the papillary dermis, near the deposits, the solar elastosis was found	1–5 mm	Long Pulsed Er:YAG Laser	Local utilization of 1% lidocaine and epinephrine. Subsequently a deep intravenous sedation was performed	6 months after the first procedure	After the full recovery the skin was free of textural changes, without any scars and dyspigmentation, no new papules were reported
Ojha et al.	83/M	Face, oral cavity within the submucosa	Negative	Few lesions on the face, white to yellow nodules on the lower lip and tongue	Amorphous and eosinophilic masses, Congo red staining was negative, PAS staining for eosinophilic material was positive	1–2 mm	Oral treatment	No needed	The patient did not show up at the follow-up	The patient did not show up at the follow-up
Voicu et al.	10/M	Nose, upper lip, cheek	Negative	Pellucid papules	Papillary findings filled with eosinophilic and amorphous cells-free masses, dilated capillary vessels were observed. Congo red staining was negative, staining with PAS was positive	2–5 mm	Oral treatment	No needed	1 month	Minor skin changes at the next visit, no sign of new lesions reported
Apfelberg et al.	47/M	Face, neck, hands	Positive	Translucent papules followed by pseudovesicles	Assemble of eosinophilic deposits, staining with PAS was positive	1–3 mm	Dermabrasion	Axillary block anesthesia	After 12 months	No relapse of colloid milium
Gomes et al.	55/M 47/M	Temples, nose, cheeks	Positive	Firm lesions characterized by yellow or translucent structure	Homogeneous findings, slightly eosinophilic	N/A	Treatment with MAL-PDT	No needed	First patient after 2 sessions, second patient after 3 extra sessions	Skin was free of lesions. No new papules developed after 1 year

*F – female, M – male, N/A – not available

Dermabrasion

In a 1978 case report by Apfelberg et al. a 47-year-old male patient presented with 1-3mm translucent papules and pseudovesicles on his face, neck and hands. Biopsies displayed eosinophilic deposits. PAS staining was positive. A rotary-powered Stryker unit with a diamond burr was used on the patient's hand under axillary block anesthesia and induced ischemia by a tourniquet. The healing process took about 14 days. After 12 months, no new skin lesions were detected.³⁵

Treatment with MAL-PDT

In a 2012 case report by Gomes et al. a 55-year-old male and his 47 year old brother presented with similar asymptomatic yellow papules on their faces. Histological examination exhibited slightly eosinophilic homogeneous masses corresponding to CM in both cases, observed in the papillary dermis. Several treatment methods were performed on both patients to address the papules on the nose, temples and cheekbones. The initial approach involved cryotherapy and photoprotective creams, but yielded unsatisfactory results. The next step included the utilization of topical photodynamic therapy (PDT). Prior to the PDT procedure, patients underwent a superficial curettage. Subsequently, a cream containing 160 mg/g of MAL (Metvix®, Galderma, Portugal) was applied to the skin and covered with an adhesive occlusive bandage for three hours. Following this, red light illumination was administered with an Aktelite® CL 128 lamp (PhotoCure ASA, Oslo, Norway). The lamp emits light with an average wavelength of 635 nm and delivers light at a dosage of light of 37 J/cm². Two PDT treatments, administered 7 days apart, led to the complete resolution of the lesions. During irradiation, the patients experienced a mild burning sensation. However, this did not necessitate the cessation of the procedure. No adverse effects, such as swelling or blistering, were observed. At a follow-up visit after one year, no relapse was reported.³⁶

Conclusion

Colloid milium is an infrequent skin condition with unknown origin. Typically, patients who develop CM have a history of prolonged exposure to sunlight, such as working outdoors on a farm or as a driver. Those exposed to chemical compounds like petroleum or hydroquinone may also develop colloid milium. While most cases of CM involve adult patients, there is some evidence of its occurrence among juveniles as well. The JCM is claimed to be inherited. The majority of skin lesions appear in sun-exposed skin areas. However, the oral cavity or tragus may also be affected. Colloid milium is not a fatal disease, but it can lead to esthetic and cosmetic concerns, prompting individuals to eliminate the papules. Treatment options for this condition are based on a few

case reports and systematic reviews. Therefore, there is no simple solution to eliminate the CM. Most databases include laser treatments, oral medications, or dermabrasion. The highest efficacy in removing lesions and preventing recurrence over time was achieved with the use of microablative fractionated CO₂ laser, non-ablative fractional resurfacing, dermabrasion, and treatment with MAL-PDT. Patients experienced remarkable outcomes, resulting in smooth skin with no visible or new lesions, and requiring a short time of convalescence. Post-treatment skincare was easy to abide or even unnecessary, and no adverse effects were reported. Satisfactory results were also obtained with the use of a long-pulsed Er:YAG laser. Nevertheless, it's worth noting that in this particular case report by Ammirati et al. the patient underwent intravenous sedation, which could pose a contraindication for certain patients.³⁴ The least effective treatment was found to be oral medication. Although it is an accessible and cost-effective solution, a case report by Voicu et al. demonstrated that its effects are minimal and might not be satisfactory.³¹ Some patients were advised to use sunscreen to minimize the influence of UV light on the skin and the development of skin lesions. However, there isn't much data on this information and further research must be conducted. The main disadvantage of the most effective solutions, such as laser treatments, dermabrasion, and MAL PDT, is their high cost. Therefore, they are less accessible to a vast majority of people. Consequently, there is a necessity to develop treatment methods for colloid milium that are not only effective and safe but also affordable.

Declaration

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Author contributions

Conceptualization, Ł.C. and M.P.; Methodology, M.P.; Software, A.K.; Validation, Ł.C., M.P. and J.F.; Formal Analysis, A.K.; Investigation, Ł.C., M.P., A.K. and J.F.; Resources, M.P., A.K. and J.F.; Data Curation, Ł.C.; Writing – Original Draft Preparation, Ł.C., M.P. and J.F.; Writing – Review & Editing, Ł.C., M.P., A.K. and J.F.; Supervision, Ł.C.; Project Administration, Ł.C., M.P., A.K. and J.F.

Conflict of interest

The authors declare no conflicts of interest.

Data availability

Not applicable.

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