MANAGEMENT OF HYPERTROPHIC AND KELOID SCARS: AN ANALYSIS OF RECENT ADVANCES AND CLINICAL CHALLENGES

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Summary

Hypertrophic scars and keloids represent a major challenge in dermatology, plastic surgery and pediatric surgery, with a significant impact on the aesthetic appearance, skin functionality and quality of life of patients. These pathological scars occur as a result of an exaggerated inflammatory response and collagen overproduction, leading to the formation of persistent fibroproliferative lesions. Despite therapeutic advances, their treatment remains difficult, with high recurrence rates. The study includes a review of the literature on current treatment strategies for pathological scars and a clinical case highlighting the recurrence of a keloid scar in an adolescent treated by surgical excision and intralesional therapy with Diprophos.

Hypertrophic scars and keloids require combined therapeutic approaches to prevent recurrence and improve aesthetic and functional outcomes. Although intralesional corticosteroids are effective in reducing fibroblast proliferation, recurrences are common. Their combination with other therapies, such as 5-fluorouracil, cryotherapy or laser therapy, could improve the success rate. In the future, biological therapies and innovative technologies, such as fractional radiofrequency therapy or stem cell therapy, could represent more effective and personalized solutions for patients with pathological scars.

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Introduction

In dermatology, plastic surgery, and pediatric surgery, hypertrophic and keloid scars are a major problem, significantly impacting the appearance, functionality of the skin, and the psychological state of patients. An abnormal inflammatory response and excessive collagen accumulation cause these pathological scars [1]. Fibroproliferative lesions are unsightly and sometimes painful.

Despite medical advances, their treatment remains challenging, as many of the available therapies have high recurrence rates and serious adverse effects. A number of recent studies, including the meta-analysis by Sha Yang et al. (2021), which examined 2009 patients from 29

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randomized clinical trials, have found that combination treatments are more effective than individual treatments [2]. Intralesional corticosteroid injection (ICI) together with botulinum toxin type A (BTX-A) or 5-fluorouracil (5-FU) was the most effective therapeutic combination found [2]. Overall, these treatments reduced scar size and recurrence rates.

In addition to traditional therapeutic strategies, Barone et al. (2021) highlight that recent research has focused on innovative therapies, such as the use of mesenchymal stem cells (MSCs), TGF-β inhibitors, and gene therapies, which may offer more effective and personalized solutions for the management of hypertrophic and keloid scars[1].

This article aims to review the latest developments in the treatment of hypertrophic and keloid scars, comparing different therapeutic approaches and highlighting the challenges encountered in clinical practice.

Material and Method

This review was conducted by reviewing the literature on the treatment of keloid scars and by presenting a clinical case illustrating the recurrence of a keloid scar in an adolescent treated with surgical excision and intralesional therapy with Diprophos.

To understand the efficacy and limitations of current treatment methods, relevant clinical trials, meta-analyses, and treatment guidelines were reviewed. This included research on the pathophysiological mechanisms of keloids, the role of growth factors (TGF-β, VEGF), injectable therapies (corticosteroids, 5-FU, botulinum toxin), and emerging alternatives such as stem cell therapy or TGF-β inhibitors.

Surgical excision remains a controversial therapeutic option in the management of keloid scars due to the high risk of recurrence, and intralesional corticosteroids, such as Diprophos, are considered standard of care to reduce fibroblast proliferation and excessive collagen synthesis [6].

Case presentation

A 13-year-old patient from a rural area, with no significant personal pathological history and no family history of abnormal scarring. He presented to the Pediatric Surgery Department of the "Sf. Ioan" Children's Emergency Hospital in Galati, presenting a keloid scar (figure 1, figure 2) on the left scapular region. In addition, the patient also presents multiple linear scars on the opposite scapula (figure 3). These appeared as a result of a traditional cupping therapy, applied to relieve muscle pain. The procedure, which involves applying heated cupping to the skin to stimulate circulation, combined with making superficial incisions, caused the appearance of local wounds on the scapula, which subsequently evolved into a progressive keloid scar.

Clinical examination

A prominent scar, approximately 15 cm x 6 cm in size, with an irregular shape and diffuse contour, is observed on the left scapula (figure 4). The color is pinkish-reddish, with discrete areas of peripheral hyperpigmentation, and the surface is firm, shiny and slightly hyperemic. The texture of the scar is dense, with a fibrous appearance, and the skin around the lesion shows slight hyperpigmentation, a sign of post-inflammatory remodeling. The patient complains of intense itching, a symptom that causes significant discomfort, being exacerbated by friction of clothes and exposure to high temperatures. The itching is caused by hyperactivity of local nerve endings and the increased release of histamine and pro-inflammatory cytokines, which indicates a persistent inflammatory process in the scar tissue. The skin around the scar also shows slight dryness, which may contribute to increased itching. On palpation, the scar is firm, with reduced elasticity, partially adherent to the deep planes, which may limit the mobility of the skin in that area. This adherence suggests a process of fibrosis extended in depth, which also explains the sensation of local tension felt by the patient. There are no signs of superinfection, such as pronounced erythema, purulent secretions or increased local temperature, and vascular exa-

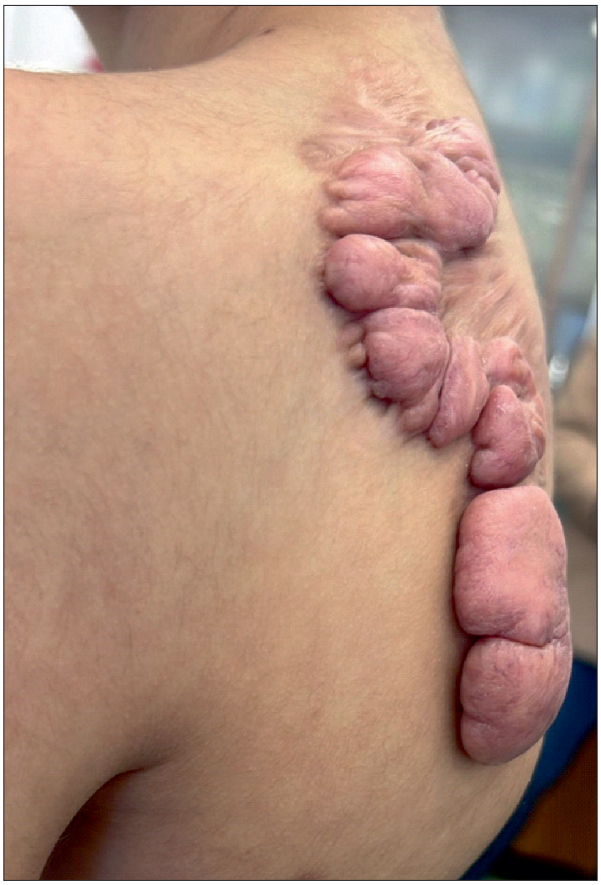

Figure 1. Extensive keloid scar on the scapula, characterized by excessive proliferation of scar tissue.

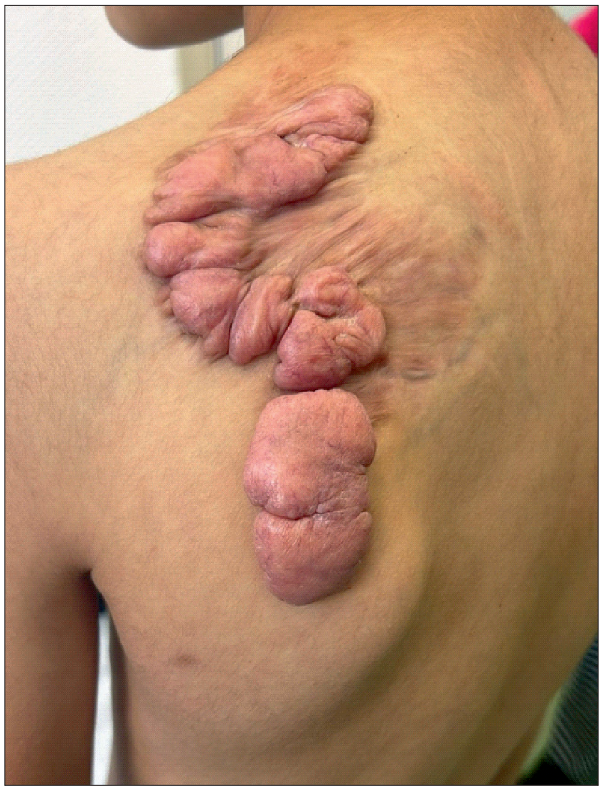

Figure 2. Extensive keloid scar on the scapula, characterized by excessive proliferation of scar tissue.

mination does not indicate ischemic phenomena or changes in local blood flow.

The patient was treated by complete surgical excision of the scar, with complete removal of fibrous tissue and adherent structures, followed by primary suture with absorbable materials to minimize local tension and the risk of recurrence (figure 4). To prevent the recurrence of the keloid, intralesional therapy with Diprophos (betamethasone) was instituted, administered weekly for twelve weeks. This therapeutic regimen aimed to reduce fibroblast activity and decrease excessive collagen production, having an essential role in limiting abnormal scar proliferation.

The postoperative evolution was initially favorable, with adequate wound healing, without immediate major complications (figure 4). In the first weeks, the patient did not report any alarming symptoms, and the appearance of the newly formed scar was optimal, with no obvious signs of hypertrophy. However, approximately 12 months after completion of treatment, the patient noticed a progressive new growth of the scar in the same area, gradually extending beyond the edges of the initial surgical wound.

The recurrent scar became progressively more prominent, presenting a firm, shiny surface and a dense consistency. The patient continued to experience persistent itching, which gradually intensified, being accentuated by contact with clothing and exposure to irritating factors. This constant discomfort was accompanied by a sensation of local tension, and the skin around the scar became rigid, suggesting the installation of an advanced fibrotic process.

The reappearance of the scar suggests a tendency for recurrence of the keloid scar, which reflects the refractory nature of the lesion to the

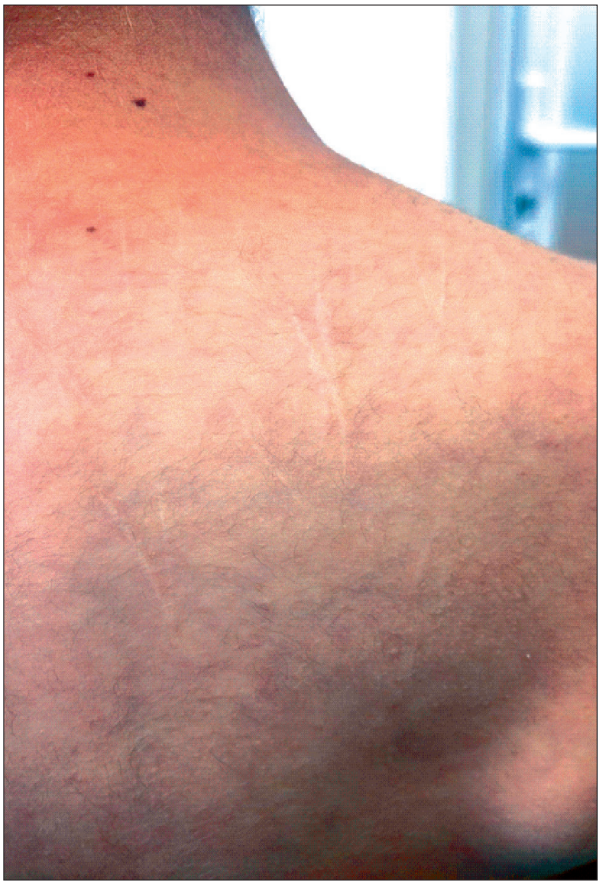

Figure 3. Discrete, linear, light-colored scars resulting from a healing process of previous injuries in the right scapular region.

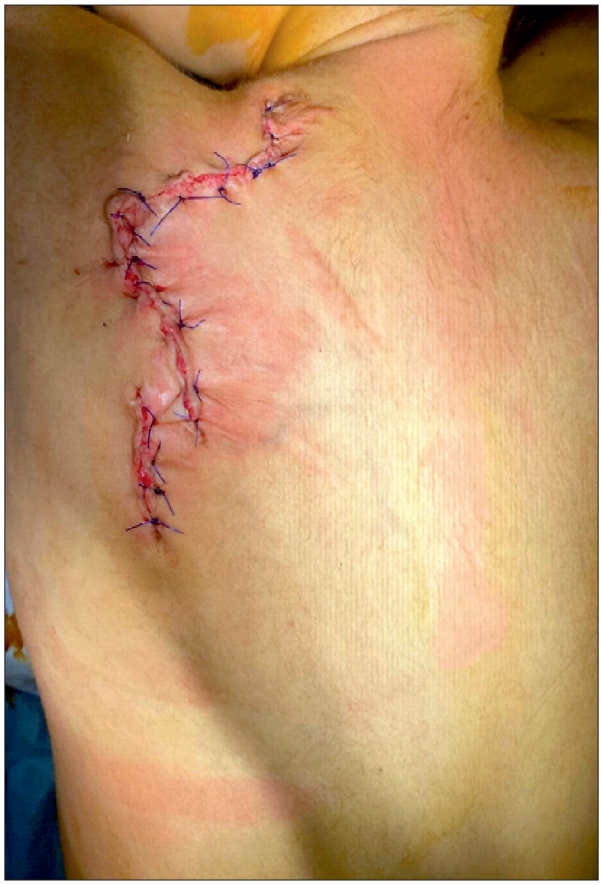

Figure 4. Post-surgical excision wound.

treatment administered. This clinical evolution highlights the difficulty of controlling the scarring process in extensive keloids, even in the presence of aggressive therapy, and emphasizes the need for additional or combined therapeutic approaches to prevent recurrence and improve aesthetic and functional outcomes.

Results

A fundamental aspect in the treatment of pathological scars is the correct differentiation between hypertrophic and keloid scars. Although both types of scars result from an abnormal healing process, they have distinct clinical characteristics. Hypertrophic scars appear shortly after the injury and develop over a period of six months. They may regress spontaneously after a year. They usually appear in areas exposed to increased mechanical stress, such as joints or areas subject to constant friction. They remain confined to the edges of the wound. In contrast, keloid scars appear three to twelve months after the trauma and continue to grow and extend beyond the edges of the original injury. More people have these scars on the earlobes, upper chest, shoulders and back.

Regarding traditional treatments, intralesional corticosteroids (ITC) remain the first line of therapy, however, their long-term use is limited by side effects, such as skin atrophy, telangiectasias and hypopigmentation. An effective alternative is 5-fluorouracil (5-FU), an antimetabolite that inhibits fibroblast proliferation and excessive collagen synthesis [1-3]. Studies have shown that 5-FU can reduce the size, but its administration is often associated with severe pain at the injection site [2].

A meta-analysis by Sha Yang et al. (2021) demonstrated that the most effective treatments are injectable combinations, with the combination of TAC with BTX-A having the highest efficacy (82.2%), followed by TAC combined with 5-FU (69.8%). The combination of silicone gel with 5-FU has also been shown to be an effective alternative for patients who cannot tolerate injections [2].

In parallel with these conventional treatments, recent research is exploring new therapeutic options, such as the use of botulinum toxin type A (BTX-A), which reduces mechanical tension on the scar and modulates the inflammatory response. Mesenchymal stem cells (MSCs) represent another innovative strategy, with the ability to promote tissue regeneration and inhibit excessive fibrogenesis [1,4]. TGF-β inhibitors and adipose tissue grafting are also promising directions, but require further studies to validate their clinical efficacy.

Discussions

The management of hypertrophic and keloid scars remains a complex challenge due to the intricate pathophysiological mechanisms involved in the formation of these scars and the variable response to treatment of each patient. Despite recent advances, there are multiple aspects that need to be considered to optimize treatment and improve clinical outcomes.

The presentation of this case highlights the complexity and difficulties of managing keloid scars, especially in young patients with a predisposition to excessive fibrosis. The recurrent scar observed in this patient suggests a pronounced tendency towards keloid scar formation, given the history of abnormal healing after the initial trauma caused by cupping therapy. Although complete surgical excision of the scar was performed correctly, the rapid recurrence of the keloid suggests persistent fibroblast activation and collagen overproduction, characteristic of this type of scar. Intralesional injection of Diprophos (betamethasone) was initially effective in reducing the inflammatory response and fibroblast proliferation, but the effects were temporary, and recurrence demonstrated that the treatment was not sufficient to prevent scar recurrence.

Another important aspect is the significant discomfort felt by the patient, especially intense itching, local tension and a feeling of skin stiffness. These symptoms are frequently reported in the case of keloid scars and can be attributed to fibroblast hyperplasia, increased number of local nerve endings and persistent inflammation in the extracellular matrix. Pruritus, in particular, is a debilitating symptom, affecting the patient's quality of life, being aggravated by friction from clothing and exposure to irritants.

In the context of recurrence, this case highlights the need for a more aggressive and individualized therapeutic strategy.

Difficulties in differentiating hypertrophic and keloid scars

One of the main obstacles in the treatment of pathological scars is the correct diagnosis and differentiation between hypertrophic and keloid scars [5]. Although both types of scars are the result of abnormal skin healing, they have distinct clinical features. Hypertrophic scars are confined to the original area of injury, may regress over time, and are more common in areas subject to high mechanical stress, such as joints or the trunk. In contrast, keloid scars extend beyond the original wound margins, do not regress spontaneously, and have a significantly higher tendency to recur. Incorrect diagnosis may lead to the selection of inappropriate treatment, which may worsen the appearance of the scar and increase the risk of complications.

The role of proinflammatory cytokines and growth factors in scar pathogenesis

The molecular mechanisms involved in the development of hypertrophic scars and keloids are complex and include aberrant regulation of transforming growth factor beta (TGF-β), interleukin-6 (IL-6), and interleukin-10 (IL-10). Studies have shown that an imbalance between TGF-β1 and TGF-β3 can contribute to excessive fibrogenesis and collagen overproduction, leading to pathological scar formation [1, 6]. This finding has led to the exploration of novel therapies targeting these molecular pathways, including the use of

monoclonal antibodies and TGF-β inhibitors. Despite theoretical promise, these therapies are still in the experimental phase and require further studies to confirm their safety and efficacy.

Current treatments and their limitations

Currently, there are numerous therapeutic options for hypertrophic scars and keloids, but each method has significant advantages and limitations.

Intralesional corticosteroids, such as Triamcinolone Acetonide (TAC), continue to be considered the first-line treatment for pathological scars due to their anti-inflammatory and antifibrotic effects. However, long-term use can cause local adverse effects such as skin atrophy, telangiectasias, and hypopigmentation [1-3]. 5-Fluorouracil (5-FU), an antimetabolite, inhibits fibroblast proliferation and collagen synthesis, offering benefits in the treatment of hypertrophic and keloid scars, but its administration is often accompanied by intense pain, erythema, and tissue necrosis, which limits its long-term use [2, 6].

Bleomycin and Interferon-α2b have demonstrated antifibrotic and antiproliferative effects, but are associated with severe systemic toxicity, including pulmonary fibrosis and significant skin reactions, which is why they are used only in selected cases, when other therapies have failed [6, 7]. Surgical excision is a viable option for large keloids, but recurrence remains common. To reduce this risk, excision is often combined with other adjuvant methods, such as intralesional administration of corticosteroids or radiotherapy [6].

Cryotherapy can be effective for small lesions, but is limited by the increased risk of hypopigmentation and recurrence. Studies show that intralesional cryotherapy is superior to external application of liquid nitrogen, with a lower complication profile [1, 5, 6]. Laser therapy is a widely used method for the prevention and treatment of scars, with effects on vascularization, fibroblast proliferation and collagen remodeling. Ablative lasers, such as CO_2 and Erbium-YAG, eliminate scar tissue and promote skin regeneration, while vascular lasers, such as PDL and IPL, reduce hyperemia and inhibit the development of pathological scars. Clinical studies suggest that early use of fractional CO_2 laser and PDL laser improves scar elasticity and reduces hypertrophy, with an optimal treatment interval of approximately five to six weeks between sessions [5, 6].

Photobiomodulation, using infrared and red light, stimulates fibroblast proliferation, increases collagen production, and reduces inflammation, and is a safe and noninvasive method [3, 7]. Photodynamic therapy combines a photosensitizer, such as aminolevulinic acid, with a light source to induce oxidative reactions that modulate the immune system, increasing the activity of macrophages and T lymphocytes. It also has an antibacterial effect, due to the destruction of the biofilm formed in chronic wounds. By stimulating angiogenesis, this therapy contributes to re-epithelialization and tissue regeneration, although further studies are needed to optimize clinical protocols [6].

Electrical stimulation reproduces the bioelectric fields involved in wound healing and accelerates this process by stimulating angiogenesis and the expression of the growth factor VEGF. It also contributes to the reduction of bacterial load, modifying the local pH, and stimulates the proliferation of fibroblasts and keratinocytes, favoring re-epithelialization and reducing inflammation.

Clinical studies demonstrate that this method can reduce wound size and has been shown to be effective in the treatment of diabetic ulcers and chronic wounds [2, 6-8]. Ultrasound therapy, used to stimulate vascularization and collagen remodeling, is divided into two categories: low-frequency ultrasound, applied in the treatment of chronic wounds due to its anti-inflammatory effect and improving blood flow, and high-frequency ultrasound, used in sports and aesthetic medicine to stimulate tissue regeneration [3].

Biological and cellular therapies represent a promising direction in the treatment of pathological scars. Botulinum toxin type A (BTX-A) reduces mechanical tension in scars and modulates inflammation, with a lower recurrence rate than corticosteroids, but its long-term efficacy requires further study. Mesenchymal stem cell (MSC) therapy may promote tissue regeneration and inhibit excessive fibrogenesis,

and experimental models suggest that MSCs may contribute to scar remodeling by reducing excessive collagen deposition and stimulating angiogenesis [1].

Intralesional verapamil, a calcium channel blocker, is also being investigated for its antifibrotic and antiproliferative properties, but current results are inconclusive [5].

In pediatric patients, the healing process presents different characteristics compared to adults, requiring tailored therapeutic approaches. Research shows that infants under six months of age heal quickly and with minimal scarring, while in children between the ages of two and adolescence, the inflammatory response is more intense, which increases the risk of hypertrophic scars. Prevention plays a key role, and treatments should be tailored to minimize the impact on skin development. Rapid wound closure, the use of fine sutures, and the avoidance of materials that can induce inflammatory reactions are important strategies to reduce the risk of excessive scarring. Non-invasive therapies, such as silicone sheets and pressure therapy, are also preferred over aggressive methods, which may have long-term side effects on growing skin [8, 9].

Conclusions

Hypertrophic scars and keloids continue to represent a major challenge in dermatology and plastic surgery, requiring complex and personalized therapeutic strategies. Although numerous treatment options exist, no single method has been proven to be completely effective, and combination therapies remain the best approach for the prevention and treatment of these scars.

Intralesional corticosteroid therapy, especially triamcinolone acetonide, associated with 5-fluorouracil (5-FU) or botulinum toxin type A (BTX-A), offers the best results in reducing scar volume and the risk of recurrence. However, corticosteroids can cause skin atrophy, and 5-FU is often associated with intense pain at the injection site.

Emerging therapies, such as botulinum toxin and mesenchymal stem cell (MSC) therapy, offer considerable promise. BTX-A reduces mechanical stress on the scar and modulates the inflammatory response, and MSCs promote tissue regeneration and reduce excessive fibrogenesis. However, these therapies are still in the research phase and require further studies before they can be implemented on a large scale.

In the case of pediatric patients, prevention plays a key role, as the risk of excessive scarring is increased in childhood and adolescence. The use of silicone sheets, pressure therapy, and rapid wound closure are essential strategies to minimize scarring.

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Conflict of interest
NONE DECLARED

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