Chapter 15
Keloids and Hypertrophic Scarring

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Keloid and hypertrophic scarring are diseases of excessive dermal fibrosis that occur during and beyond the wound healing process. These lesions are difficult to treat as they have a high tendency to recur. Affected individuals often deal with physical disfigurement, discomfort, and negative psychological impact. Keloid scarring was initially documented in Western literature in 1806. However, the Yoruban culture of Nigeria had described the typical characteristics of keloids in 3000 B.C. in both oral literature and art. Their descriptions demonstrated an understanding of the genetic nature of keloids, their tendency for unchecked growth, and their lack of response to attempted treatment [1].

Human conceptions of scarring are often deeply tied to social and cultural beliefs. While individuals in Western societies often strive to minimize scarring, cultures in regions throughout sub-Saharan Africa view cicatrization as a valued symbolic process or respected ornamentation. Both men and women intentionally prolong the healing process of inflicted wounds through regular reinjuring, packing of wounds with foreign agents, and superficial exposure to environmental substances, such as tree sap and wood [2].

Though research is slowly elucidating the pathophysiology of this condition, much still remains to be understood about keloid scarring and effective treatment options.

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Epidemiology

The highest rate of occurrence of keloid scarring is between the ages of 10 and 30 years old, with men and women affected equally [3, 4]. Although keloid scarring can occur in any skin type, it most commonly occurs in darker pigmented skin. The highest incidence has been reported in the African and Hispanic population at 16% [5, 6]. Rates have been found to increase during pregnancy and puberty [4].

Clinical Presentation

Keloids typically develop after trauma, including cuts, surgical wounds, burns, and inflammatory lesions such as acne (Fig. 15.1). Spontaneous keloids also can occur. Early on, keloid lesions are soft and erythematous. However, over time, they become firm [7]. While darker skin type keloids tend toward hyperpigmentation, lighter skin type keloids can be more telangiectatic [8] (Fig. 15.2).

Keloids most commonly develop on the central chest, upper back, ears, and shoulders. Those in areas of high tension, such as the central chest, tend to be flat and more broadly based. However, shoulder and back keloids generally grow larger than other areas. Keloids on the face, neck, wrist, and lower extremities are less common. The jawline, however, is still at high risk for keloid and keloid-variant development. Scalp keloids tend to be papulonodular [9].

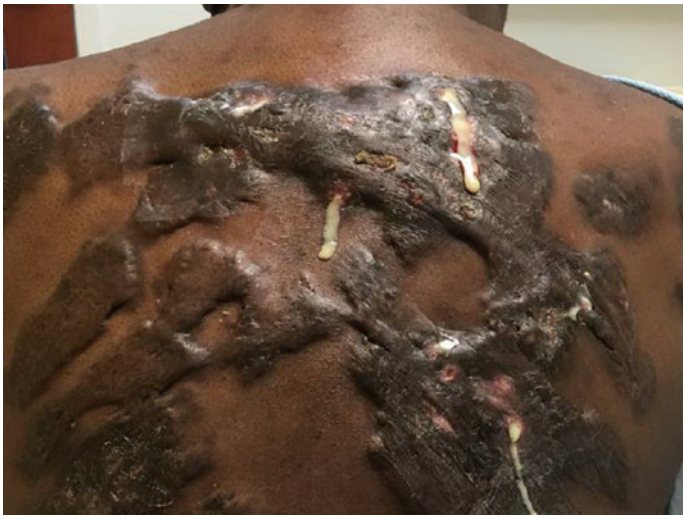

Fig. 15.1 Extensive firm hyperpigmented plaques on the back secondary to severe acne in a FST V woman

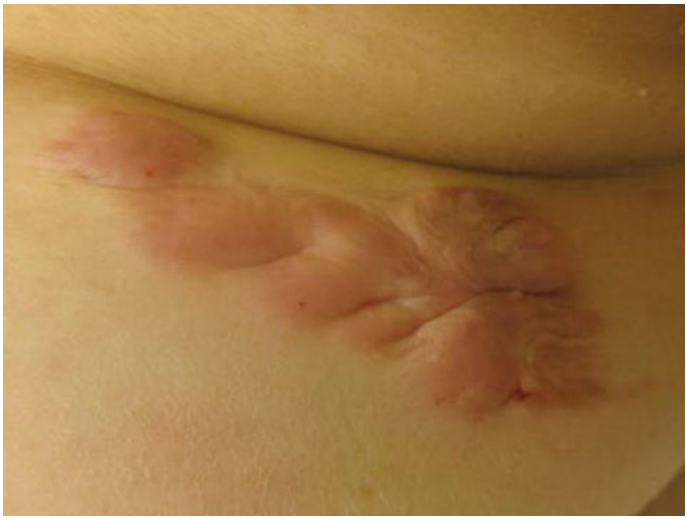

Fig. 15.2 Pink brown telangiectactic and hyperpigmented multilobulated plaque in a FST III Asian woman

There are four morphologies of keloids that develop on the earlobe. The button-shaped keloid is a single nodule that occurs on the anterior or posterior aspect of the earlobe. In the dumbbell morphology, both anterior and posterior keloid nodules are present, and a central stalk connects them. In contrast, in the wraparound presentation, the keloid is "U-shaped" so there is no central stalk (Fig. 15.3). Finally, the lobular form is complete replacement of the lobe by a single large lesion due to recurrent keloids [7].

The consideration of keloids and hypertrophic scars as more than a matter of appearance has grown in recent years, since both conditions can be quite symptomatic. They can become pruritic and painful, particularly during periods of growth. The pruritus can be attributed to the increased quantity of mast cells and histamine within HTS and keloid tissue [10]. Twenty-five percent of affected individuals state their symptoms are severe. Further, these symptoms can have a negative impact on quality of life, most severely in emotional well-being. Pruritus and pain have been found to have the strongest effect on quality of life, beyond that of cosmetic issues such as color, thickness, and irregularity [11].

Hypertrophic Scars Versus Keloids

Hypertrophic scarring is an important clinical entity to differentiate from keloids. Both types of conditions are triggered by injury, including cuts, surgical wounds, burns, and inflammatory lesions such as acne [7].

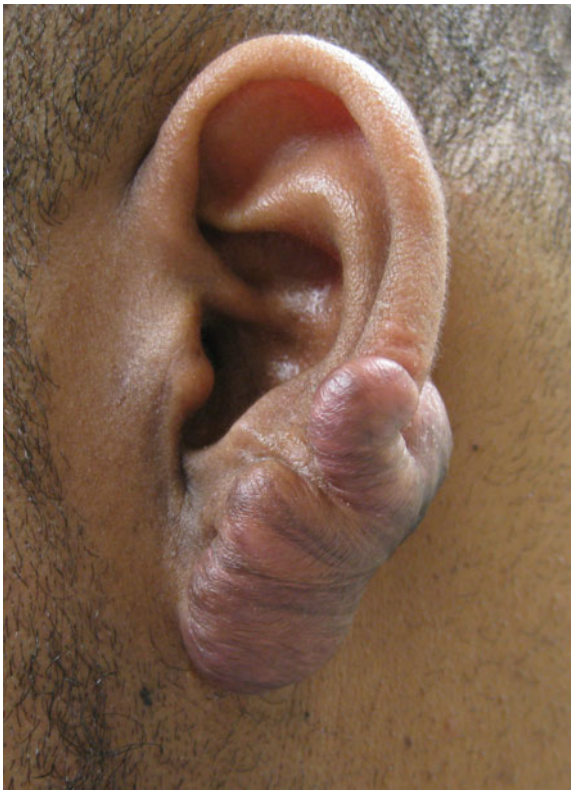

Fig. 15.3 Wraparound firm hyperpigmented auricular keloid in a FST V man

Like keloids, hypertrophic scars are elevated and often erythematous scars. However, they typically appear pink or white and remain confined to the borders of the original wound. Further, after a period of growth they tend to stabilize in size or shrink over time.

On the other hand, keloids are a more aggressive form of scarring. They typically are a deep red or purple color and extend beyond the borders of the original wound in an irregular fashion [5], giving rise to the originally described "claw-like" borders [12]. Keloids tend to have more erratic growth patterns. Periods of stability in size and inflammation can quickly be followed by reactivation and growth [3].

Predisposing Factors

Trauma is the most well-documented trigger for keloid development, and as such vaccinations, tattoos, and piercings can all lead to keloid scarring. Individuals with a predisposition to acne and keloids are at particularly high risk for keloid

development on the chest, back, and jawline. Thus, it is important to aggressively manage acne early in at-risk individuals [13].

Hormonal influences can also contribute to keloid and HTS development, which explains their increased incidence during puberty and pregnancy [3]. Prolonged wound healing, through infection, injury, or presence of foreign material in the wound, can also predispose to pathologic scarring. The most important identified extrinsic risk factor, aside from any initial inciting trauma, is mechanical tension and strain. Scars that are perpendicularly oriented to the direction of skin tension from underlying muscle contraction are at high risk for becoming hypertrophied. As a result, the chest, particularly the presternal area, shoulder, and back are particularly prone to the development of these scars [3]. The earlobes are also at high risk to develop keloid scarring, likely related to the common practice of ear piercing. Early piercing can minimize the risk in this highly reactive area.

Histology

Both keloids and hypertrophic scars are processes of increased dermal extracellular matrix deposition. In young lesions, type III collagen predominates; however, over time replacement with type I collagen occurs [5].

In normal skin, collagen is arranged in bundles that lie parallel to the skin surface in an organized pattern. In hypertrophic scars, collagen bundles maintain this directionality but are more loosely organized, shorter, and arranged in a wavy pattern [14]. In keloids, the collagen is even less organized, with apparent loss of bundle structure, larger fibril size, increased fibril density [15], random orientation of collagen fibrils, and unpatterned connections between fibers [14].

Hypertrophic scars and keloids both have increased vascularity compared to normal skin and normal scars. The vessels have greater volume density, are dilated, and take longer and more tortuous paths in the papillary and reticular dermis [14, 16].

Hypertrophic scars have a thickened epidermis and increased cellularity [16]. Myofibroblasts are characteristically increased. Collagen, fibroblasts, and small vessels are randomly organized within nodular structures in the deep dermis [14, 16, 17]. Both keloids and HTS have absent dermal papillae and cutaneous appendages. In keloids, rarely, nodular collagen structures can be seen [16].

Genetics

As there are high rates of occurrence in pigmented populations, increased rates of concordance in identical twins, and reports of familial clustering, a genetic link is suspected for keloid scarring [18–20]. Autosomal dominant inheritance with incomplete penetrance and variable expression is the most commonly reported

pattern, although autosomal recessive and autosomal dominant with complete penetrance has also been described [20–24].

Many major histocompatibility (MHC) alleles have recently been implicated in keloid scarring, particularly DRB1*15, HLA-DQA1*0104, DQB1*0501, and DQB1*0503 [25]. SMAD-3, 6, and 7, genes reported to be involved in other fibrotic disorders, did not correlate with risk for keloid scarring in Jamaican patients [18]. However, a Chinese pedigree linkage study showed keloid association with 19q21.1, potentially involving SMAD in keloid pathogenesis [26]. Other studies have found varying levels of SMAD subtypes associated with keloids [27]. A systematic review showed several commonly significantly dysregulated genes in keloids. The top processes controlled by the most commonly implicated genes were related to skeletal development, biological adhesion, and cell adhesion. Meanwhile, the top processes controlled by the gene mutations in HTS were ossification, extracellular matrix structural constituents, and the extracellular region [28].

Pathophysiology

The pathogenesis of keloids is poorly understood. Multiple studies have shown abnormal levels of transforming growth factor-β (TGF-β) in keloids and HTS. The pro-scarring forms, TGF-β1, TGF-β2, and their receptors, are increased, and the anti-scarring form, TGF-β3 and its receptor, is decreased in this tissue [29]. Fibroproliferative cytokines, such as IL-6, have increased expression and levels [30]. Aberrant Wnt signaling and platelet-derived growth factor levels have been found in keloids and HTS, while IL-8, homeobox13, and early growth response-1 all increase fibroplasia [31].

Other drivers may include increased levels of S100A8/9 proteins [32], elevated p53 levels [33], high-mobility group box protein-1 (a pro-fibroblastic proliferation cytokine), imbalanced levels of matrix metalloproteinases (collagenases), and altered Vitamin D levels or cellular signaling relating to it [34]. Systemic hypertension and elevated body mass index have also recently been postulated to contribute to keloid scarring [35, 36].

In vitro, fibroblasts in the superficial and basal regions of keloids have been found to have similar population doubling times and saturation densities as normal fibroblasts. However, central keloid fibroblasts have half the apoptotic rate of normal fibroblasts and reach higher cell densities [37]

Variants

Keloid variants including acne keloidalis nuchae (AKN) and pseudofolliculitis barbae will be discussed in brief below. Please refer to the chapter on adnexal disorders a full review.

Acne Keloidalis Nuchae

AKN is a keloid variant that was initially coined in 1869 as dermatitis papillaris capillitii [38]. Most commonly, black men under the age of 50 are affected, and after the age of 50 affected individuals usually do not develop new lesions [39]. Similar to true keloids, they present with pain and pruritus [39]. The condition begins after puberty as an acute folliculitis and perifolliculitis; however, with time, it progresses into a chronic condition. Initially, the condition presents with 2–4 mm firm papules, which resemble keloids, and pustules on the base of scalp and back of the neck. The pustules often break open from pruritus-induced scratching or hair brushing. Over time, the papules can merge to form large horizontally oriented plaques. Complications include subcutaneous abscesses with draining sinuses and a scarring alopecia of the affected skin. The keloid-like papules and plaques are nonresponsive to antibiotic therapy, which can treat the underlying folliculitis [38].

The pathogenesis of AKN is unknown. Short tightly curled hair, which is common in the African American population, is believed to be the incriminating factor in AKN. As the hair shaft grows beyond the surface of the epidermis, it curls back and pierces the skin surface. This triggers an inflammatory reaction in the epidermis leading to the development of the characteristic papules and pustules. Other triggers include constant rubbing in the area from shirt collars, a chronic folliculitis, and an autoimmune condition [38].

Histologic evidence in one study found AKN to be a scarring alopecia. Foreign antigens, such as the demodex mite and normal skin flora, and autologous antigens, such as sebum, on the follicular epithelium and intrafollicular canal can trigger an inflammatory cascade. This leads to damaged and fragmented hair unit structures that can encourage HTS and keloid scarring [40]. AKN has also been described as a transepithelial elimination disorder [41], a form of lichen simplex chronicus [42], and associated with the male seborrheic constitution, increased fasting blood testosterone, and early reproductive years [43].

Pseudofolliculitis Barbae (PFB)

The term pseudofolliculitis of the beard was first coined in 1956 [44]. The condition primarily occurs in African American men as well, likely because of its association with tightly curled coarse hair types. The prevalence in this population is 45–83%. However, women and other ethnicities can also be affected. In fact, women of African or Hispanic lineage with hypertrichosis or hirsutism have similar incidence of PFB [39].

PFB presents with inflammatory papules and pustules in the beard area. The papules can be flesh-colored, erythematous, or hyperpigmented. Typically, the upper lip and lateral margin of the face are spared. Other shaved areas can also develop PFB, such as the scalp and leg [38]. In fact, in predisposed women, these lesions may occur in the axilla and groin [39].

As PFB is a result of epidermal and dermal inflammation from curled hair shaft growth, shaving is the precipitating factor in its development. Two mechanisms explain its pathogenesis: extrafollicular penetration and transfollicular penetration. Transfollicular penetration occurs when the hair is shaved against the grain with the skin held taught. Once the stretch on the skin is released, the hair tip withdraws below the skin surface. Curved hair regrowth results in penetration of the follicle wall, leading to the development of papules and pustules. Hair removal techniques that can cause midshaft hair breakage, such as tweezing and electrolysis, can also lead to transfollicular penetration. In extrafollicular penetration, the shaved tip grows in a curved fashion beyond the hair follicle, repierces the epidermis, and then grows into the dermis. The inflammatory response that occurs on epidermal penetration is significantly heightened with the hair shaft's presence in the dermis. This gives rise to the characteristic papules and pustules. The hair springs back out of the skin once it has grown roughly 10 mm long [38]. Injury of PFB lesions from shaving can lead to secondary bacterial infection, abscesses, hypertrophic scarring, and keloids [38].

Prevention

Primary Prevention

Minimizing trauma is the most important method of prevention. High-risk patients, including those with a greater degree of skin pigmentation, family history, or personal history of keloids, should avoid tattoos, piercings, and other surgical procedures [45]. To avoid auricular keloid development, ear piercing before 11 years of age is advantageous [46]. The senior author, however, prefers piercing before seven years of age given the changing hormonal milieu of earlier onset puberty may increase the risk for keloid formation.

Prevention plays a major role in the treatment of AKN and pseudofolliculitis barbae. For AKN, patients should avoid high-collared shirts and hats, which can irritate the scalp. Also, short hairstyles and razor/hair clipper use along the occipital scalp should be avoided [39]. For PFB, patients should not pull the skin taught when shaving and should shave in the direction of hair growth. Regular brushing of the beard can help free embedded tips [38].

Secondary Prevention

Ear Keloids

Ear lobe keloids typically respond well to postsurgical pressure therapy. The recommended regimen is continuous pressure of 24–30 mm Hg for eight to 24 hours over 6- to 12-months [6]. In 1436 keloids, magnets as a form of pressure therapy

worn 12 hours daily for 6 months showed a recurrence rate of 11.6% after 18 months. Interestingly, recurrence was associated with high body mass index, prior treatment, and slow keloid growth rate [36]. Postsurgical "sandwich" radiotherapy and triple therapy with surgical excision, intralesional steroid, and silicone sheeting have also been utilized [47, 48].

Pressure Dressings

Pressure has been postulated to lead to collagen and fibroblast degeneration in HTS via creation of a hypoxic environment [19]. Changes in cytokine expression may underlie structural changes induced by pressure garments in HTS [49]. In an animal model study, 2 weeks of pressure treatment led to 51.9% decreased collagen levels in HTS, most significantly through reductions in collagen I and III [50]. Rearrangement of collagen fibers from nodular to wave-like patterns also occurs. Increased dermal layer apoptotic indices, reductions in dermal cell layer density, and significant reductions in myofibroblast and α-smooth muscle actin levels have also been found [51].

For years, compression garments have been standard practice in many institutions for the prevention of burn-induced HTS [52]. However, a 2009 meta-analysis found little convincing evidence for the effectiveness of pressure garment treatment [53]. Optimum pressure requirements are also unknown. Some papers have shown 15 mmHg is required at minimum for improvement [54, 55] and 40 mmHg can lead to complications [55]. A 12-year randomized control trial published in 2011 did find efficacy of pressure therapy as a preventative modality for burn induced moderate to severe HTS [56]. Further, studies in keloids specifically are limited.

Silicone Gel Sheets

Silicone gel sheets (SGS) are often used as preventative treatment of high-risk wounds. Primarily, SGS provide occlusion and hydration to the healing wound, key components of wound healing. Transepidermal water loss in the stratum corneum, which is increased in unoccluded scar, stimulates keratinocyte production of cytokines. These active fibroblasts produce exaggerated amounts of collagen, which assist in water retention. Occlusion of the developing scar with SGS therefore stunts excessive collagen and cytokine production [57–59]. Specifically, TGF-β1, TGF-β2, bFGF, and PDGF are decreased with preventative SGS use in early scars [58, 60]. It is important to note that excessive occlusion and hydration can impair wound healing [57]. SGS provide a similar level of occlusion as normal skin, explaining their ability to improve collagen structures and cytokine profiles.

Secondly, wound tension is lowered with SGS application. Tension is transferred from the wound to the sheet through the sheet's adhesion to the surrounding skin [57]. Thirdly, friction between the scar and SGS produces a negatively charged electric field that improves collagen orientation and encourages scar involution

[61]. Finally, decreased injury may be incurred on healing skin with the gentle adhesive of SGS [57, 62, 63].

Application of SGS is recommended for 12–24 hours daily with twice daily washing for at least 1 month. Application should be initiated 2–3 weeks after wound formation to allow for wound epithelialization. SGS use as preventative treatment has been shown to improve scar size, induration, pruritus, and pain [64–66]. However, a recent systematic review, concluded that the benefit of preventative SGS in high-risk patients does not currently exist as most studies are of poor quality [67].

Silicone gel preparations form a clear, gas-permeable, water-impermeable, silicone covering on the skin. Several advantages exist for gel preparations over SGS, including ease of application over large areas of skin, near joints, and on cosmetically sensitive areas such as the face. Compliance tends to be higher as patients prefer the decreased visibility of gel preparations to SGS. Further, there is less risk of infection and rash with gel since the need for regular washing and cleaning of a reusable sheet has been removed [59]. Prospective RCTs have found decreased scar elevation, erythema, pliability, and symptoms with the preventative use of gel preparations in high-risk lesions [68–71]. Further, no significant difference in the efficacy between SGS and silicone gel has been found [70]. Silicone gel formulation efficacy is still debated given the unclear overall benefit of SGS use [67].

Radiation

Improvements in keloids with postoperative radiation therapy are believed to be via regulation of the fibroblast cell cycle. Radiotherapy extends the G0/G1 phase of the cell cycle and normalizes the rate of fibroblast apoptosis [37, 72]. Further, expression of genes associated with cellular senescence, mainly p16, p21, and p27, is upregulated with treatment [72].

Concerns about the carcinogenic potential of radiation have limited the use of radiotherapy for keloids [73]. External beam radiotherapy is the most commonly utilized technique for postoperative treatment. However, it is difficult to treat long wounds and wounds on uneven skin surface through this technique. Interstitial and superficial brachytherapy are alternative methods in which the radiation source, an applicator, is placed within or just above the lesion, respectively. These are well suited for irregularly contoured lesions, such as those on the scapula or jaw. Interstitial treatment allows for a smaller irradiated area, thus less involvement of healthy issue. However, radiation schedules must be much shorter given the implanted applicator must be removed to prevent wound dehiscence and keloid recurrence. On the other hand, superficial brachytherapy allows for more cost-effective and shorter treatment regimens, as well as more consistent radiation dosage to changing wound shapes secondary to postoperative edema and hematoma [74, 75].

Overall, high-level randomized studies are lacking [76]. Prospective clinical studies have shown recurrence rates with radiotherapy after surgical excision from 2.2 to 38.0% [74, 75, 77–81]. Improved long-term control has been demonstrated

with radiotherapy initiation within 24 hours of surgery [80]. Rates of improvement in pruritus and pain are notable. Side effects include hypopigmentation, hyperpigmentation, erythema, pruritus, skin atrophy, telangiectasia, and subcutaneous fibrosis [75, 78]. There may be heightened risk of the development of pigment abnormalities in higher Fitzpatrick skin types [81]. It has been reported that a dosage range of 10–30 Gy for keloids has a low risk of carcinogenesis while maintaining efficacy in keloid treatment [82]. However, a dosage of 15 Gy is reported effective for 90% of keloids [79], and total doses above 21 Gy increase the risk of side effects such as abnormal pigmentation [83]. None of the reviewed studies reported any incidences of cancer; however, follow-up time periods ranged from 18 to 46.5 months [74, 75, 77–81]. Additional well-structured randomized control trials with longer follow-up periods are still needed to assess the efficacy and carcinogenesis risk of radiation therapy. The elevated risks in adolescents and children must be considered prior to decision for radiation treatment.

Treatment

Corticosteroids

Although there are only a small number of well-designed studies on corticosteroid efficacy, intralesional corticosteroid injections have continued as the gold standard in keloid treatment since the 1960s [6, 84]. By inhibiting expression of TGF-β, VEGF, and IGF-1, corticosteroid treatment is able to prevent overgrowth of fibroblast populations and excessive collagen formation [6]. Corticosteroids induce G1 cell cycle arrest but do not promote apoptosis [85].

Typically, the regimen is a 10–40-mg/mL injection every 1–2 months (Table 15.1). Response rates range from 50 to 100% with recurrence rates of 9–50% [86]. Topical steroids have not shown the same efficacy and are therefore not preferred [84]. Recently, delivery of topical steroid through fractional ablative laser has shown potential for post-acne keloids [87]. Side effects of corticosteroid therapy include dermal and epidermal atrophy, telangiectasia, hyper- and hypopigmentation. As children are most at risk for developing Cushing's syndrome from intralesional corticosteroids, total dosage should not exceed 30 mg per month in children [88]. For post-excision prophylaxis in helix keloids, no significant advantage was found in recurrence rate with the addition of two postoperative injections of triamcinolone to a single intraoperative injection [89].

Surgical Excision

Because recurrence rates range from 45 to 100%, surgical excision as a monotherapy is discouraged [90–92]. AKN is the only type of keloid that typically

Table 15.1 Clinical practice—intralesional corticosteroids

1. Pain control
a. Options: topical or combination anesthetics, intralesional or perilesional anesthetic, cryotherapy
b. Senior author prefers to avoid IL lidocaine as injections are painful and IL anesthetic can limit the volume of injected corticosteroid
c. Cryotherapy should be used with care. Epidermal melanocytes are more sensitive to cryotherapy destruction than keratinocytes or fibroblasts. Excessive cryotherapy can lead to hypopigmentation
2. Preparation
a. 27–30 gauge needle on a 1 cc syringe. Larger needle sizes may exacerbate injection pain and lead to leakage of injected medication
b. Use of luer lock needle syringe that is fully locked to the needle. High backpressure is exerted from the dense keloid tissue during injection. This can cause needle separation from the syringe
c. Begin with triamcinolone 10 mg/mL. Increase by 10 mg/mL if there is not adequate response
d. Always wear a mask
3. Injection procedure
a. The needle should be inserted bevel down
b. Senior author prefers a fan technique: several tracks within the body of the keloid should be made with each needle insertion. Deliberate medication injection should be done at the edges of the keloid
c. Throughout the entire injection, medication should be released against the resistance of the keloid tissue only. Any superficial or deep release of corticosteroid may lead to epidermal or subcutaneous atrophy, respectively, and hypopigmentation
d. To avoid injection pain from dulled needle, the needle should be changed every four to five injections
4. Patient counseling
a. Patients should be educated that treatment will involve a series of at least five to six injections every four to eight weeks
b. Side effects should be discussed: depressions secondary to atrophy, color changes, telangiectasia
c. If side effects occur, there is an option to skip an injection in the series or continue onwards depending on patient preference

has low recurrence rates after excision, even with secondary intention healing [6]. Intraoperative pathologic examination is not routinely performed for keloids. However, incomplete excision of keloid tissue, either at peripheral or deep margins, and ill-defined keloid tissue borders pose an increased risk of recurrence [93]. In certain situations such as auricular keloids, intralesional excision with rind flap use has shown benefit in areas where total scar excision and closure will distort structural anatomy. This method also reduces wound tension and leaves behind rich vasculature for the healing wound [47, 94]. Combined treatment with surgical excision and intralesional corticosteroids, pressure devices, magnets, or postoperative radiation improves recurrence risk. Auricular keloids respond particularly well to surgical excision with adjuvant therapy (See Section on Ear Keloids).

Cryotherapy

By inducing blood stasis and coagulation, cryotherapy destroys the microvasculature supplying keloid tissue [95]. It also can cause directly cellular damage, although the fibrous tissue itself has been found to be relatively resistant to freezing [95, 96]. Histologic analyses have found cryotherapy normalizes collagen synthesis, orientation, and fibroblast differentiation [96, 97]. Small keloids tend to respond best and multiple sessions may be required for adequate keloid response. Side effects include pain, atrophy, and ulceration. Given melanocyte sensitivity to cooler temperatures, there is also a high risk of hypopigmentation, particularly in higher Fitzpatrick groups [98, 99].

In contrast to surface cryotherapy, intralesional cryotherapy, a relatively recent method, enables more direct damage to dermal fibrous tissue with sparing of superficial tissues. Thus, there is a decreased risk of melanocyte damage and hypopigmentation. Keloid and hypertrophic scars have shown improvements of 47–89% with monotherapy [97, 99–102]. Combination treatment with topical silicone gel sheeting has not improved success rates [101], although a recent study with addition of intralesional corticosteroids demonstrated a volume reduction of 93.5% [95].

Lasers

Both ablative and non-ablative lasers have been utilized for keloid treatment, including pulsed dye laser (PDL) (585–595 nm), neodymium-doped yttrium aluminum garnet (Nd:YAG) (1064 nm), erbium-doped yttrium aluminum garnet (Er:YAG), and CO_2. The use of ablative lasers, including Er:YAG and CO_2, have been limited due to high recurrence rates. There is no agreement on the mechanism of action for each of the lasers, although multiple theories exist. A level 1 systematic review recently found the evidence for laser treatment for keloids was not strong enough to endorse its efficacy during the treatment and follow-up periods [103].

Pulsed Dye Laser (PDL)

By the late 1980s, PDL had become a leading treatment for vascular lesions, including port-wine stains and telangiectasias. Soon after, a landmark study by Alster et al. paved the way for its use in HTS and keloids [104, 105]. Multiple mechanisms have been suggested for scar improvement with PDL use. The leading theory is based on the selective targeting of hemoglobin, which causes local thermal injury to the blood vessel with minimal energy dispersion to surrounding tissues [106, 107]. Coagulation and occlusion of the microvasculature in the papillary and reticular dermis follows. The ischemia and nutrient deprivation of the scar tissue

inhibits its growth and collagen production. PDL is also believed to stimulate matrix breakdown via inhibition of TGF-β and PDGF and stimulation of MMP and IL-6 [106]. Collagen fiber structural realignment through heat-induced modifications of disulfide bonds has also been suggested [108].

Both 585 and 595 nm are utilized for keloid treatment, although more studies have been done utilizing 585 nm [107]. PDL should be used cautiously in darker pigmented patients, as it can target the epidermal pigmentation and lead to greater risk of complications. For these patients and those with scars in high-risk areas, the energy density should be decreased by 10%. Posttreatment purpura is the most common side effect, which typically resolves within 10 days [109]. No correlation has been found between energy density and treatment outcome. Thus, higher fluence may pose unnecessary risk for irritation without additional treatment benefits [103]. A recent systematic review of PDL treatment in HTS and keloids included studies with PDL of 585 nm wavelength, duration of 250–1500 ms, spot size of 5–10 mm, and fluences of 3.5–9 J/cm^2. PDL was superior to conventional modalities in improving overall scar appearance and scar pigmentation. Issues with incomplete outcomes, selective reporting, blinding, and/or randomization in these studies limited the ability to formulate a strong conclusion about PDL for HTS and keloids [108].

Nd:YAG

Nd:YAG treatment is believed to function through heat generation. This initiates an inflammatory cascade, elevating vascular permeability, MMP production, and collagen degradation [106]. The resulting tissue infarction causes skin sloughing with underlying wound healing. 532-nm lasers are the most efficient frequency for use, possibly because this energy level is close to the absorption peak of oxyhemoglobin (542 nm). This leads to the greatest energy absorption by hemoglobin and consequent vascular destruction. A recently published retrospective case series on use of 1064 nm Nd:YAG laser in 102 patients with HTS or keloids found both scar types significantly improved in subjective and objective parameters. However, keloid recurrence rates 6 months after a 1-year regimen were still high—4% on the abdomen, 25% on the scapula, 35.7% on the upper arms, and 52.9% on the anterior chest [110].

Other Lasers

CO_2 treatment induces reorganization of collagen bundle structures [111, 112], decreases in type I collagen, and may increase type III collagen [113]. CO_2 laser treatment may also improve keloids through modulation of MMP9 levels [111]. Further high level studies are needed for CO_2 and copper bromide lasers.

Onion Extract

The exact mechanism of onion extract, *Allium cepa*, activity is still unknown. In vitro fibroblast studies have shown onion extract inhibits fibroblast proliferation, decreases β1 integrin, and can induce fibroblast apoptosis. β1 integrin is an adhesion protein important in fibrogenesis. It may also inhibit IL-6 and VEGF [114], upregulate MMP-1 production [115], and modulate histamine levels by increasing mast cell stability [116]. Results of onion extract studies have been mixed. While unchanged rates of keloid development with topical 10% onion extract in silicone gel have been found [117], improved scar volume and induration has also been found in combination with 0.5% hydrocortisone [118]. Topical mixtures of onion extract with other compounds have improved pain, sensitivity, pruritus, elevation, and neoangiogenesis [119, 120]. These improvements may be confounded by a large representation of HTS in study participants and impact of heparin on collagen fibril structure [119].

Chemotherapeutics

Multiple chemotherapeutics have been utilized for keloid treatment, including 5-fluorouracil (5-FU), mitomycin, and bleomycin. 5-FU is a pyrimidine analogue with antimetabolite activity. It induces G2-cycle arrest and apoptosis, perhaps through p53 activation [85]. Theoretically, its antimetabolite activity should be greatest on fibroblasts stimulated to proliferate and secrete collagen. Thus, 5-FU as a preventative modality may be more efficacious than as a treatment modality. Excessive 5-FU can lead to erythema, scar widening, ulceration, and wound dehiscence [121, 122]. In a recent study, the prophylactic use of post-excisional 5-FU (50 mg/mL) and botulinim A toxin injections in treatment-resistant keloids had a recurrence rate of 3.75% after 2 years [122]. As a treatment modality, treatment with 5-FU tattoo (50 mg/mL) elicited greater reduction in keloid height, induration, and pruritus than intralesional triamcinolone alone (40 mg/mL) [123]. 5-FU treatment is effective in 45–79% of patients and up to 96% of patients with combination 5-FU and triamcinolone [121]. Of note, low doses of triamcinolone have been used, from 1:45 to 4:45 triamcinolone:5-FU. The current evidence cannot define a maximum allowed dose per scar area or total. However, most studies have investigated weekly injections, 80–100 mg of 5-FU per session, and a 4:45 mg/mL ratio of TAC:5-FU. This is therefore the current recommended frequency, concentration, and dose [124].

Bleomycin and mitomycin are both cytotoxic proteins produced by *Streptomyces* species [125, 126]. However, studies on both are limited. There is some evidence of the efficacy of intralesional bleomycin in flattening keloids and providing symptomatic control [127–129]. When used intralesionally with electroporation, which increases medication absorption by over 10,000-fold, bleomycin has also improved keloid scar [127]. Atrophy and hyperpigmentation have been reported as long-term

side effects [127]. Systemic side effects of bleomycin, mainly pulmonary, renal, and cutaneous fibrosis have not been found with keloid treatment [128, 130, 131].

Calcium Antagonists

Intralesional verapamil was initially harnessed for burn scar therapy in 1994 [132]. In vitro studies with fibroblasts have shown calcium antagonists slow extracellular matrix growth by hindering proline incorporation [133], inhibiting IL-6 and VEGF production [134], and inducing collagen degradation [133–136]. A recent systematic review and meta-analysis agreed on lack of high quality studies examining calcium antagonist efficacy [137, 138]. In the three existing high-level studies, verapamil had efficacy equal to or greater than that of intralesional triamcinolone [139–141]. While verapamil had a slower rate of improvement, it also had a significantly decreased rate of complications and a lower drug cost [139, 141].

Botulinum Toxin Type A

There has been some recent interest in intralesional botulinum toxin type A as a treatment modality. Although it can eliminate the constant wound margin tension that induces fibroblast growth [86], in vitro studies have shown conflicting evidence of any adjusted expression of chemical messengers [142, 143]. Independently, it has shown efficacy in improving scar size [144], and it may be equally as efficacious as corticosteroids with a lower risk of side effects [145].

Key Points

1. High-risk groups for keloid development include adolescents, young adults, pregnant women, and darkly pigmented populations, including blacks and Hispanics.
2. Acne lesions and areas of high tension, such as the chest, shoulder, and back, are also at higher risk for keloid development. Aggressive management of acne in predisposed populations is important in prevention.
3. AKN and pseudofolliculitis barbae are keloid variants in which curled hair shaft growth leads to cutaneous injury and inflammation.
4. Ear piercing below 11 years of age is preferable to prevent auricular keloids.
5. Intralesional triamcinolone (10–40 mg/mL) is the gold standard in treatment. Auricular keloids often respond well to combination therapy with surgical excision.

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