Keloid—An Update
Shehzad A Khan, MD

Introduction
A keloid is defined as a benign growth of dense fibrous tissue developing from an abnormal healing response to a cutaneous injury, extending beyond the original borders of the wound or inflammatory response (1). Described by Egyptian surgeons as early as 1700 BC, it was Baron Jean-Louis Alibert (1768-1837) who identified keloid as an entity. He called them cancroide, later changing the name to cheloide to avoid confusion with cancer. The word is derived from the Greek chele, meaning crab’s claw, and the suffix -oid, meaning like (2). Keloids gain significance from the fact that not only are they frequently symptomatic but often become a cosmetic nuisance. Though they are benign and non-contagious many patients are affected both physically and psychologically and report a severe negative impact on quality of life (3).

Incidence
Though the reasons are unknown, keloids occur more frequently among Blacks, Hispanics and Asians and less commonly in Caucasians (4,5) There is a fifteen times higher frequency of occurrence in highly pigmented people (2).

Some tribes are known to cause keloids intentionally either for decoration or as a ritual. In Sudan for eg women of the Nubia-Kush are intentionally scarified with facial keloids as a means of decoration. In New Papa Guinea the people cut their skin and stuff clay or ash into the wounds so as to develop bumps (known as keloids or weals). This painful ritual then enables them to be celebrated for their courage (2).

Pathogenesis
Keloids have a complex pathogenesis with both genetic and environmental factors being responsible. They develop subsequent to injury or inflammation of the skin, but the exact pathogenesis is still unknown. Keloids most often occur in the setting of surgical or non-surgical wound healing (like lacerations and earlobe piercing). Inflammatory skin conditions such as chickenpox infection, acne vulgaris, folliculitis, or vaccinations (mainly BCG vaccination) may induce keloid formation. Though they often develop months after a wound or inflammatory process, they can develop as late as a year later (4). Many patients may not recall an inciting traumatic event or inflammatory process (“spontaneous keloids”) and this may have occurred in response to some form of inflammatory process perhaps forgotten or unrecognized by the patient.

Keloid-derived fibroblasts have been found to be involved in aberrant expression of various growth factors like VEGF, TGF-β1, TGF-β2, CTGF, as well as the PDGF-α receptor (6,7). Relationship between these over expressed growth factors and pathologic scarring has been the focus of research recently. It was Capaner et al. who reported that over expression of TGF-β1 is an important component in the formation of keloids, but is not a sufficient as an independent factor, giving credence to the theory that keloid formation is a multifactorial process (8). Compared to normal dermal fibroblasts, fibroblasts derived from keloids exhibit increased production of collagen and matrix metalloproteinases (9). A delicate balance of increased collagen production and breakdown of tissue facilitated by matrix metalloproteinases is needed for proper wound healing. Analysis of the proliferation rate of keloid fibroblasts versus those derived from hypertrophic scars revealed an increased rate among keloid fibroblasts (10). It is believed that the negative feedback mechanism whereby the excessive fibroblast activity is dampened to prevent exuberant repair in normal scars is defective (11). As of now, no specific gene has been linked to the development of keloids. Most cases occur sporadically, although the finding of a positive family history is not unusual (12). It is likely that multiple genes impart susceptibility to keloid development, with different genes contributing to keloid formation in different families. It is held that analysis of multiple genes by microarray technology to compare gene expression among keloids and normal scars can be of great help for understanding the genetic control of keloids (13).

Age and Sex
Keloids can affect people of all ages but is most commonly found in ages between ten and thirty years. Children under 11 are less likely to develop keloids, even when they get their ears pierced (2). Though keloids affects both sexes , the incidence in young female patients has been reported to be higher than in young males, possibly due to the greater frequency of earlobe piercing among women (14).

Clinical Features

Fig 1. Keloid on the chest of a teenager after burns from a gas stove.

Clinically keloids present as firm nodules which can be flesh colored, hypopigmented or erythematous secondary to telangiectasia. The lesion is often located over the site of a wound, injury or other lesion (15). They should not be confused with hypertrophic scars which are raised scars that do not grow beyond the boundaries of the original wound and may reduce over time (2). Frequently symptomatic, most of the patients with keloids have
pain or pruritus. In a study by Lee et al it was found that more than eighty per cent patients of keloids had pruritus and around fifty per cent experienced pain (16). They may not improve in appearance over time and can limit mobility if located over a joint (2).

**Location**

Common sites of involvement include the chest, shoulders, upper back, back of the neck and earlobes (17). In addition unusual cases of keloids that have been reported are those following severe burn injury (18), at the sites of vaccination (19), genital keloids following circumcision or trauma (20-23), and corneal keloids following corneal trauma (24).

**Management**

A wide variety of therapies exist for the treatment of keloids. However none is completely effective. In one large meta-analysis of thirty nine studies where twenty seven different treatments were used, it was found that the chance of clinical improvement with any type of treatment was seventy per cent (25). The different modes of therapy are as follows:

**Intralesional Drugs**

*Intralesional steroid injection:* This is the most common modality used to treat keloids. It has a very good tolerability and effectiveness in alleviating the symptoms. Triamcinolone acetonide is usually used at a concentration ranging from 10 to 40mg/ml depending on the size and location of the lesion. The dose is started usually at 40mg/ml for lesions on the trunk or extremities and then titrated accordingly at subsequent visits. It has been shown to inhibit collagen synthesis and fibroblast growth in vitro (26). Pretreatment with topical lidocaine has been found to be effective in ameliorating injection-associated pain (14). Studies have shown a fifty percent recurrence rate with intralesional steroids (27-31). Complications of such therapy include skin atrophy, hypo- or hyperpigmentation, and the development of telangiectasias.

*Intralesional Bleomycin:* Small trials have shown significant improvement in keloids with intralesional bleomycin (32,33). However, larger trials and longer follow ups are needed to establish their long term efficacy.

*Intralesional Interferon Alpha 2b:* Since interferons may increase collagenase activity, they have a therapeutic potential for keloids (34). However recent studies using intralesional interferon alpha 2b have not found it to be an effective treatment as an adjunct to excisional surgery (35).

**Surgery**

Surgical excision provides immediate cosmetic correction but has a high recurrence rate (36). Following excision, recurrence of keloids can be prevented by plastic closure of the skin including techniques such as v-plasty or w-plasty which reduce skin tension (2) Following surgery, adjuvant therapy with topical Imiquimod or Mitomycin C (37) have shown some benefit. Factors that are associated with the best surgical outcomes are excellent wound edge closure, combining minimal tension with maximal eversion and ensuring incisions are made along relaxed skin tension lines (38). Surgery runs the risk of leading to a longer scar and a potential larger keloid in case of recurrence (39).

**Cryotherapy**

It is an excellent mode of therapy for keloids which are small and occur on lightly pigmented skin. It freezes the skin and causes sludging of the circulation beneath, effectively creating an area of localized frostbite. It acts by altering collagen synthesis and inducing keloidal fibroblast differentiation towards a more normal phenotype (40). Using cryotherapy just prior to steroid injection in order to induce edema and thus facilitate steroid injection has been advocated by some (41). Drawbacks include hypopigmentation in dark-skinned patients, considerable pain and prolonged healing following treatment (14).

**Radiotherapy**

Different techniques of radiotherapy that can be employed are superficial x-rays, electron beam, and low- or high-dose rate brachytherapy (42). Electron beam radiation can be used at levels which do not penetrate the body deeply enough to affect internal organs. Orthovoltage radiation is more penetrating and slightly more effective. Post-excisional radiotherapy is typically employed immediately following surgical excision. When combined with excision, efficacy rates are higher, ranging from 65 to 99 percent (43). In one retrospective study assessing the efficiency of 15-Gy-electron beam irradiation with more than 18-months follow-up, a recurrence free success rate of 77 percent was reported (44). Adverse effects of radiation therapy include transient erythema, hyperpigmentation and an extremely low risk of carcinogenesis (45,46). Due to the uncertainty of the risk, it is recommended by some authors to limit radiotherapy to those who have failed previous excisional treatments and to patients 21 years of age or older (47).

**Laser Therapy**

Overall the results of laser therapy are not very encouraging. The best results have been seen with the use of the 585nm pulsed dye laser (PDL) (48,49). Combining PDL with intralesional steroids helps to soften the lesion and augment the integration of steroid (50). Using carbon dioxide and argon lasers has a high recurrence rate of 90%. Using the Nd:YAG laser as a monotherapy or in combination with intralesional triamcinolone injection has shown good results with a large percentage of patients remaining keloid-free at follow-up (51).

**Dressings**

Moistened wound coverings made of silicone gel or silastic form a non-invasive and relatively inexpensive adjunctive mode of treatment for keloids. The silicone gel sheets act by providing an occlusive barrier. They soften scars by enhancing hydration thus reducing erythema pain and pruritus (52). The silicone sheets are applied after surgical excision as soon as re-epithelialization is achieved and are worn for at least 12 hours per day (4). Such
sheets last for around 10 to 12 days and can be washed and reapplied (53). An international expert panel has recently recommended silicone gel sheet therapy as a first line prophylaxis following surgical excision (36).

Other Drugs

Contractubex Gel: This gel has shown exceptional results in keloids especially newer ones. These gels contain allium cepa extract, heparin and allantoin. Prognosis is supposed to be better if treatment is initiated earlier. Some authorities consider it now to be the first line of approach in conservative treatment of keloids.

Imiquimod Treatment: Imiquimod is FDA approved topical immunomodulator for the treatment of certain warts and actinic keratoses. Since it is known to reduce collagen production in fibroblasts by upregulating proinflammatory cytokines it has been studied as adjunct to surgical therapy (54, 55). Though short term results are encouraging, the overall clinical benefit is not clear due lack of long-term follow up and smaller numbers treated.

5-Fluorouracil: Numerous studies have shown that 5-FU is not better than other modalities and is associated with significant adverse side effects (56-58).

Prognosis

Though keloids are not dangerous, they do cause cosmetic disfigurement. Sometimes they may reduce in size over time. On the other hand removal or reduction may be temporary and surgical removal may result in a bigger keloid (15).

Conclusion

Keloids may recur with a median of more than 12 months following treatment, thus follow up at 6 months could potentially overestimate the efficacy of treatment. Follow-up for any keloid intervention should extend to at least 1 year (59), and perhaps even as long as 2-3 years (60).

Prevention

There is an increased risk of developing abnormal scars in those patients who have a previous keloid or have a family history of keloids. They should be advised not to go for body piercing or elective cosmetic procedures with a risk of scarring. To prevent recurrence following surgery adjunctive measures like use of silicone gel sheets should be taken.

References

20. Erdemir F: A rare complication after circumcision: Keloid of the penis. Int Urol Nephrol 2006,

Conflict of Interest: None

Author Information:
Shehzad Ahmed Khan, MD
Senior Consultant, Internal Medicine
Kashmir Health Services
Srinagar, Kashmir, India
Pin: 190001
Email: drshehzadkhan@yahoo.com