KELOID A DERMATOLOGICAL DISORDER : A REVIEW

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Summary

Keloid which means "crab claw", is a type of scar, which depending on its maturity, is composed of mainly either type III (early) or type I (late) collagen. It represent a form of pathologic wound healing affecting a substantial segment of world population. A keloid scar is benign, non-contagious, and sometimes accompanied by severe itchiness and pain., and changes in texture. In severe cases, it can affect movement of skin. The rate of occurrence of Keliod is reported to be predominantly higher in Black and Asian populations. Keloids remain one of the most challenging dermatologic conditions to successfully treat and may have significant psychosocial impact for the patient. In this review, we have discussed the pathogenesis, genetics, causes, signs and symptoms, diagnosis, treatment and prevention of Keloid.

Keywords: Collagen ,Keloid (KD), Scar – hypertrophic.

Introduction

The term Keloid was originally described in the 1800s as Cheloid, which is derived from the Greek root chele, which means "crab claw"[1]**.** It is a type of scar, which depending on its maturity, is composed of mainly either type III (early) or type I (late) collagen. It is a result of an overgrowth of granulation tissue (collagen type 3) at the site of a healed skin injury which is then slowly replaced by collagen type 1. Keloids are firm, rubbery lesions or shiny, fibrous nodules, and can vary from pink to flesh-coloured or red to dark brown in colour. A keloid scar is benign, non-contagious, and sometimes accompanied by severe itchiness and pain.[2], and changes in texture. In severe cases, it can affect

movement of skin. The rate of occurrence of KD is reported to be predominantly higher in Black and Asian populations.The increased familial clustering in KD, its increased prevalence in certain races and in identical twins suggest a strong genetic predisposition to keloid scar formation. Nevertheless, KD appears to be genetically heterogeneous, with both dominant and recessive modes of inheritance having been reported.Genetically susceptible individuals form keloid scars after wounding but not at every body site A number of precipitants have been reported including chicken pox, burns, surgery, tattoos, bites, lacerations, piercing and vaccination, but not all such insults lead to a keloid scar even in the susceptible individual. KD can occur at any age, but typically commence between the ages of 10 and 30 years, and tend to be less common in the very young and the very old. It has been suggested that KD develops most commonly during puberty. Younger people are presumed to have a higher frequency of trauma than older individuals. This is thought to be due to a greater skin tension in young compared to older skin, which is less tense and more redundant but all demographic data tend to be based on sufferers who request medical advice. KD is a heterogeneous disease, both in terms of its morphology and its clinical behaviour. Thus, analysis of its natural history from both the pathological and epidemiological points of view becomes important. This is of particular significance due to the ill-defined treatment of KD despite a range of therapeutic modalities and high rate of recurrence.[3]

ALTERNATIVE NAMES

Hypertrophic scar; Keloid scar; Scar - hypertrophic

HISTORICAL BACKGROUND

The first recognized description of keloids was in the Smith Papyrus around 1,700 BC. Among the cases described, case 45 describes the "existence of swelling on his breast, large, spreading, and hard. Touching them is like touching a ball of wrappings." Since the Middle Ages, ancient African artwork has depicted the formation of keloids for ornamental purposes. In 1802, Alibert provided a review of keloids. He coined the term cheloides to describe the lateral extensions often observed, which resembled the legs of a crab growing into normal tissue. He observed keloids arising both spontaneously and after trauma. As well, he differentiated between keloids and scars that remained within the confines of the initial trauma, currently referred to as hypertrophic scars. Despite an increased understanding of wound healing and collagen metabolism, the exact cause, clinical behavior, and optimal treatment of keloids and hypertrophic scars remain an enigma. [4]

PATHOGENESIS

The pathogenesis of keloid formation is poorly understood, but keloids generally occur after injury or inflammation of the skin in predisposed individuals. Commonly reported causes of keloids include acne, folliculitis, chicken pox, and vaccinations in addition to more obvious trauma (such as, earlobe piercing, lacerations, or surgical wounds). Keloids may develop as early as 1 to 3months after trauma or inflammation, but some may occur up to 1 year after the inciting event.Keloids generally do not occurwith small needle sticks such as local anesthetic injection unless they provoke inflammation (eg, vaccination sites). In one study, approximately 10% of Taiwanese teenagers who received BCG vaccination were reported to have a keloid at the injection site. Occasionally, patients may report the spontaneous development of a keloid, but because keloids represent the end product of aberrant wound healing, this likely represents a lack of recall or trivial trauma that was unnoticed by the patient. Fibroblasts derived from keloids overproduce type I procollagen, express higher levels of vascular endothelial growth factor (VEGF), transforming growth factor-(TGF-) b1/b2, platelet derived growth

factor-(PDGF-)a receptors, and have reduced growth factor requirements in vitro. Ladin et al reported that keloidal fibroblasts have lower rates of apoptosis, and others have demonstrated a down-regulation of apoptosis-related genes. Cultured keloidal fibroblasts have been found to have increased production of collagen and matrix metalloproteinases compared with normal dermal fibroblasts.
The proliferation rate of keloid fibroblasts is increased compared with hypertrophic scars. A built-in negative feedback mechanism, as yet not well understood, prevents an excessive buildup of fibroblasts in normal scars. Bronson et al reported that fibroblasts derived from mature scars were able to suppress the in vitro proliferation of fibroblasts in normal wound healing. As such, it seems quite plausible that aberrant healing of wounds in hypertrophic scars and keloids is secondary to an inability to activate or respond to the negative feedback mechanism in place to suppress fibroblast activity. In this setting, fibroblasts would essentially be allowed to brun-amok,Q resulting in raised, enlarged, and cosmetically significant scars[1].

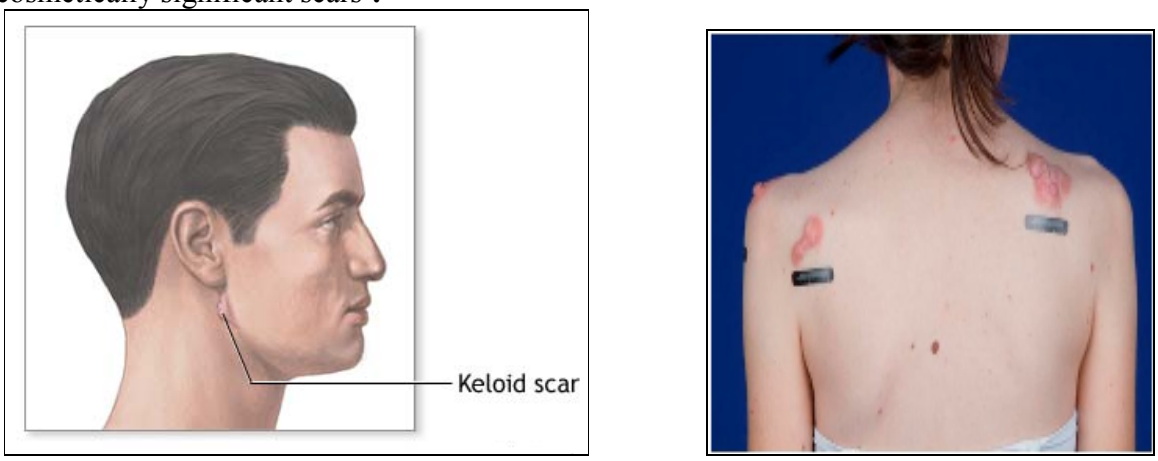

Figure 1: Pathogenesis of Keloid

GENETICS

The etiology of keloids likely involves genetic and environmental factors. Although many cases occur sporadically, a positive family history is not uncommon. There are no clearly defined genetic loci conferring risk for keloids. Genetically it is associated with HLA-B14, -B21, HLA-BW16, -BW 35, HLA-DR5, -DQW3, blood group A. Transmission reported as autosomal dominant and autosomal recessive [5].

KELOID COMPOSITION

Compared with normal skin, keloids have been reported to contain the following: Increased quantities of water, calcium, histamine, acid phosphatase, alanine transaminase, lactic dehydrogenase, o~ globulins (oq-anti- trypsin, a2-macroglobulin), fibronectin and fibronectin messenger RNA (mRNA), elastin, glycosaminoglycans, proteoglycans (chondroitin-4-sulfate), soluble collagen, collagen deposition (type VI), galactosylhydroxylysyl glucosyl transferase, proline bydroxylase, transforming growth factor (TGF-~I) abnormal collagen cross-linkages . Decreased quantities of procollagen polypeptides because of increased degradation. Increased, decreased, or same quantities of collagenase, collagen type III . Increased or same quantities of collagen type I, ratio of collagen type I to type III, type I procollagen-speeific mRNA . Same quantities of types I, II, III, IV, V procollagen-specific mRNA

HISTOPATHOLOGY

Histologically, keloids are characterized by increased collagen and glycosaminoglycan content[6]. There are whorls of thickened hyalinized collagen bundles that are classically described as keloidal collagen. This irregular orientation of collagen is distinct from normal tissue where collagen bundles are in parallel to the epidermis. Keloid rather than hypertrophic scar shows : the absence of prominent vertically oriented blood vessels, the presence of a tongue-like advancing edge underneath normal-appearing epidermis and papillary dermis, a horizontal fibrous band in the upper reticular dermis, and a prominent fascia-like band [7].

CAUSES [8]

It occurs only in people who are predisposed to it, i.e. have a tendency to form keloids. Keloids occur from such skin injuries as:

- Acne
- Burns
- Chickenpox
- Ear piercing
- Minor scratches
- Surgical cuts
- Traumatic wounds
- Vaccination sites

They are fairly common in young women and African Americans. Keloids often run in families. Keloidosis is a term used when many or repeated keloids occur.

SIGNS AND SYMPTOMS[9]

Keloids are raised and look shiny and dome-shaped, ranging in color from pink to red. Some keloids become quite large and unsightly. Aside from causing potential cosmetic problems, these exuberant scars tend to be itchy, tender, or even painful to the touch.

A skin lesion that is

- Flesh-colored, red, or pink
- Located over the site of a wound or injury
- Lumpy (nodular) or ridged

The lesion may itch while it is forming and growing.

DIAGNOSIS

Keloids are characterized by excessive deposition of collagen in the dermis beyond the boundaries of the wound, whereas hypertrophic scars remain within those boundaries. However, it can be difficult to distinguish between early keloids and hypertrophic scars. Unlike hypertrophic scars, which usually regress in a year or two, keloids typically grow for several years and then become stable. There are, however, some Keloids that grow for years or even the lifetime of the patient. Also, although hypertrophic scars respond well to therapy, keloids may not[10].

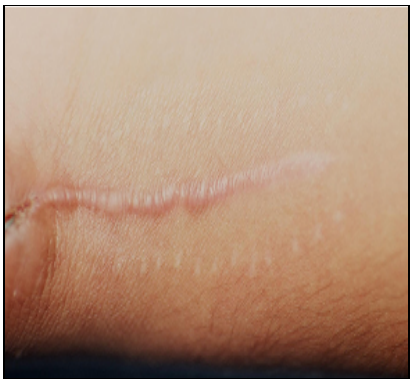

Figure 2: Hypertrophic scar of the forearm

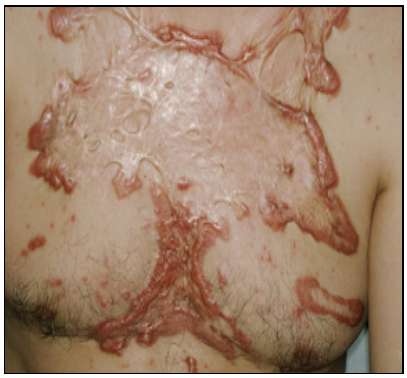

Figure 3: Kelloid on the chest that has been growing for 15+ years

TREATMENTS [11,12,13,14,15]

The best treatment in patients with a known predisposition.

1	**Preventing unnecessary trauma or surgery** (including ear piercing, elective mole removal)
2	**Any skin problems in predisposed individuals** (eg, acne, infections) should be treated as early as possible to minimize areas of inflammation.
3	**Intra-lesional corticosteroids** are first-line therapy for most keloids. A systematic review found that up to 70 percent of patients respond to intra-lesional corticosteroid injection with flattening of keloids, although the recurrence rate is high in some studies (up to 50 percent at five years)
4	**Excision** Scalpel excision may be indicated if injection therapy alone is unsuccessful or unlikely to result in significant improvement. Excision should be combined with preoperative, intraoperative, or postoperative triamcinolone or interferon injections . Recurrence rates from 45 to 100 percent have been reported in patients treated with excision alone; this falls to below 50 percent in patients treated with combination therapy
5	**Silicone gel sheeting** has been used for the treatment of symptoms (eg, pain and itching) in patients with established keloids as well as for the management of evolving keloids and the prevention of keloids at the sites of new injuries. A systematic review of controlled trials found some evidence that silicone gel sheeting may reduce the incidence of abnormal scarring, but concluded that any estimate of effect was uncertain because the underlying trials were of poor quality and highly susceptible to bias . Treatment with silicone gel sheeting appeared in some studies to improve elasticity of established abnormal scars, but the evidence was again of poor quality and susceptible to bias.
6	**Cryosurgery** is most useful in combination with other treatments for keloids . The major side effect is permanent hypopigmentation, limiting its use in people with darker skin.
7	**Radiation therapy** have found to be highly effective in reducing keloid recurrence, with improvement rates of 70 to 90 percent when administered after surgical excision. A small randomized trial of treatments after surgery found recurrences in two of sixteen earlobe keloids (13 percent) treated with radiation therapy and in four of twelve earlobe keloids (33 percent) treated with steroid injections. However, concern regarding the potential long-term risks (eg, malignancy) associated with using radiation for an essentially benign disorder limits its utility in most patients. Radiation therapy may occasionally be appropriate as treatment for keloids that are resistant to other therapies. In addition, radiation therapy may be indicated for lesions that are not amenable to resection.

8	**Interferon alfa** injections may reduce recurrence rates postoperatively. However, all currently available studies of interferon therapy suffer from methodologic problems, making an evidence-based recommendation regarding its use difficult .
9	**Pulsed dye laser** treatment can be beneficial for keloids, and appears to induce keloid regression through suppression of keloid fibroblast proliferation, and induction of apoptosis and enzyme activity. Combination treatment with pulsed dye laser plus intralesional therapy with corticosteroids and/or fluorouracil may be superior to either approach alone[].

Table 1: Treatment for Keloid

PREVENTION

You can prevent discoloration from sun exposure by covering the forming keloid with a patch or Band-Aid, and by using sunblock when spending time in the sun. Continue these extra protection measures for at least 6 months after injury or surgery for an adult, or up to 18 months for a child.Imiquimod cream has recently been used to prevent keloids from forming after surgery, or to prevent keloids from returning after surgery to remove them.

POSSIBLE COMPLICATIONS

- Cosmetic changes that affect the appearance
- Discomfort, tenderness of the keloid
- Irritation from rubbing on clothing or other forms of friction
- Limited mobility (if the keloids are extensive)
- Psychological distress if the keloid is large or disfiguring
- Return of the keloid

FUTURE RESEARCH

There is a need for further research to determine the etiology of keloids. Unfortunately, there is no animal model for research. Hoof animals do develop keloid-like lesions on their extremities, as do eagles and the vulture family of birds.However, in these animals, the lesions clear without therapy when the offending agent is withdrawn.

Conclusion

Keloid a type of scar, which can be benign, non-contagious, and sometimes accompanied by severe itchiness and pain and changes in texture. In severe cases, it can affect movement of skin.Inshort keloid is an rare dermatologically skin disorder .Prevention is vital, and newer therapy will likely prove to be most effective in the treatment of keloids.

References

1. David T. Robles, MD, PhD, Daniel Berg, MD, Abnormal wound healing: keloids Clinics in Dermatology, 2007, 25, 26–32.
2. Ogawa R. The Most Current Algorithms for The Treatment and Prevention of Hypertrophic Scars and Keloids. Plast Reconstr Surg. 2010125: 557-568,.

3. A. Bayat, G. Arscott a , W.E.R. Ollier, D.A. Mc Grouther, M.W.J. Ferguson, Keloid disease: clinical relevance of single versus multiple site scars, The British Association of Plastic Surgeons 2005 58, 28–37
4. .Sandy S. Urioste, Kenneth A. Arndt, and Jeffrey S. Dover, Keloids and Hypertrophic Scars: Review and Treatment Strategies, Seminars in Cutaneous Medicine and Surgery, 1999, 18 (2) :159-171.
5. Brian Berman, MD, PhD, and Harlan C. Bieley, MD Miami, Florida, Keloids, J Am Acad Dermatol 1955;33:117-23.
6. Berman B, Flores F. The treatment of hypertrophic scars and keloids. Eur J Dermatol 1998;8:591 – 5.
7. Lee JY, Yang CC, Chao SC, et al. Histopathological differential diagnosis of keloid and hypertrophic scar. Am J Dermatopathol 2004; 26:379- 84.
8. Rapini, Ronald P.; Bolognia, Jean L.; Jorizzo, Joseph L. Dermatology: 2007, 2-Volume Set. St. Louis: Mosby.
9. Ogawa R. The Most Current Algorithms for The Treatment and Prevention of Hypertrophic Scars and Keloids. Plast Reconstr Surg. 125: 557-568, 2010.
10. A. Paul Kelly, MD. Update on the Management of Keloids. Semin Cutan Med Surg 28:71-76
11. Shaffer JJ, Taylor SC, Cook-Bolden F. "Keloidal scars: a review with a critical look at therapeutic options.". J Am Acad Dermatol, 2002, 46 (2): 63–97.
12. Berman B, Bieley HC "Adjunct therapies to surgical management of keloids". Dermatologic Surgery , 1996, 46 (2): 126–130.
13. O'brien L, Pandit A, "Silicon gel sheeting for preventing and treating hypertrophic and keloid scars.". Cochrane Database Syst Rev. 2006 , (1): CD003826.
14. Sclafani AP, Gordon L, Chadha M, Romo T "Prevention of earlobe keloid recurrence with postoperative corticosteroid injections versus radiation therapy: a randomized, prospective study and review of the literature.". Dermatologic Surgery 1996, 22 (6): 569–574.
15. Asilian A, Darougheh A, Shariati F . "New combination of triamcinolone, 5-Fluorouracil, and pulsed-dye laser for treatment of keloid and hypertrophic scars". Dermatologic Surgery , 2006, 32 (7): 907–915.