Management of Keloid: An Updated Overview

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Introduction:

In the 19th century, Jean Louis Alibert, the father of French Dermatology, first described the keloid as 'les cancroïdes' then changed the name into 'chéloïde' to avoid confusion cancer. This term is derived from the Greek word (khçlçé) for crab's claw [1].

Keloid is a dermal fibroproliferative disorder that occurs due to abnormal wound healing and is characterized by excessive collagen deposition. It occurs due to skin injury as trauma, insect bite, burns, surgery, vaccination, skin piercing, acne, chickenpox, and herpes zoster infection, which reach the reticular dermis, but sometimes it may occur spontaneously [2]. Most keloids develop within 3 months of skin injury, but some may develop after 1 year [3]. Besides cosmetic disfigurement, it may be associated with pain and pruritis, which affects the quality of life in patients [4].

Keloid and hypertrophic scars:

Compared to a hypertrophic scar, keloid develops slowly over months beyond the initial wound edges, while hypertrophic scar develops over weeks within the initial wound edges. Keloid consists of the random organization of Type I and Type III collagen fibers, while hypertrophic scars consist of an organized parallel Type III collagen. The hypertrophic scar may heal spontaneously over the years, unlike keloids [5].

Risk factors:

Keloid may develop anywhere except in mucous membranes, but it develops more in ear lobes, sternum, deltoid region, and pubic area. The incidence is higher in the second and third decade and during pregnancy due to sex hormones (androgen and estrogen) that cause vasodilatation that increases inflammation [6]. Also, hypertension causes severe keloids by the destruction of the blood vessel and increase inflammation [7].

Racial factors include dark-skinned African, Asian, and Hispanic individuals who have a higher keloid development incidence than Caucasians. It ranges from 4.5% to 16% [8]. In 5%–10% of cases, familial keloids are due to autosomal dominant mode of transmission with incomplete penetrance and variable expression on chromosomes 2 and 7 [9].
Keloid is a clinical diagnosis so unusually sent for further analysis by the pathologist. The hallmark of a keloid is keloidal collagen which is a thickened eosinophilic hyalinized collagen bundle. Other findings include a "Tongue-like" advancing edge below the papillary dermis, the horizontal fibrous band in the upper reticular dermis, and prominent fascia like a band in the deep dermis [10].

**Pathogenesis of keloid:**

The pathogenesis of keloid disease is still unknown. Many theories have been proposed, but none of these theories have been proven. Keloid is considered the end product of an abnormal wound healing process.

**Phases of wound healing:**

*Inflammatory phase:*

It follows the onset of trauma. Homeostasis is achieved by blood vessel vasoconstriction and platelet plug formation. Local mast cells release chemical factors to attract polymorphonuclear leukocytes and macrophages [11].

*Proliferative phase:*

It starts after 2-3 days and lasts for 3-6 weeks. The homeostatic plug is replaced by granulation tissue. The granulation tissue is formed of fibroblasts, macrophages, procollagen, elastin, proteoglycans, and hyaluronic acid. Macrophages release growth factors as transforming growth factor-β (TGFβ), platelet-derived growth factor (PDGF), connective tissue growth factor (CTGF), epidermal growth factor (EDGF), and vascular endothelial growth factors (VEGF). PDGF and TGF-β activate fibroblasts and stimulate collagen type III and extracellular matrix (ECM) formation. VEGF induces angiogenesis resulting in the formation of immature blood vessels [12].

*Maturation phase:*

It is called the remodeling phase and may last for one year. In this phase, collagen type 3 is replaced by stronger collagen type 1, arranged in bundles in the dermis, not in basket wave as the normal unsacred dermis. Immature blood vessels undergo regression. Contraction of the scar tissue is mediated by the action of myofibroblasts [13].

*In keloid:*

a) Dermal injuries as burns or trauma trigger immune cells on aberrant wound healing.

b) Macrophages and other immune cells increase inflammation and promote scar formation.

c) Growth factors as VEGF and PDGF stimulate chemotaxis, angiogenesis and fibrosis.

d) Myofibroblasts increase collagen synthesis and retard cell migration, thus resulting in excessive scarring.

e) Keloidal fibroblasts have a higher proliferative activity and lower apoptosis rates than normal fibroblasts. This results in the overproduction of collagen and cytokines. Collagen production in keloids is twenty times greater than normal skin and three times greater than a hypertrophic scar.

**Management:**

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Different modalities of keloid management had been discussed but achieving a satisfactory result is challenging and may require combinations of different modalities.

A-injections

1-Intralesional corticosteroid:

Many injectable steroids are available in the treatment of keloid, including hydrocortisone acetate (25 mg/mL), dexamethasone (4 mg/mL), and methylprednisolone (4 mg/mL). Still, triamcinolone acetonide (TAC) (40 mg/mL) is the most commonly used either alone or in combination with other therapy [14].

TAC is a fluorinated derivative of prednisolone with four times as potency as hydrocortisone, but with less solubility, so it remains active at the injection site for a longer time [15]. The rate of improvement ranges from 50% to 100%, with a recurrence rate ranging from 33% to 50% after 1 to 5 years [16]. According to practitioners’ protocol, the recommended dose for TAC in keloid is 10 to 40 mg/mL. The intralesional steroid side effects include local side effects such as pain, telangiectasia, skin and subcutaneous lipoatrophy, leukoderma, post-inflammatory hyperpigmentation, and ulcerations [17]. Systemic side effects may include Cushing syndrome with adrenal insufficiency, a rare and serious side effect that occurs in children after a single session with 40 mg of TAC; thus, care must be taken during administration of TAC in children with multiple or large lesions [18].

2-5-Flourouracil:

5-Flourouracil (5-FU) is a fluorinated pyrimidine analogue that inhibits nucleic acid synthesis by disrupting the conversion of uridine into thymidine by inhibiting the thymidylate synthase enzyme. It also has antimetabolite activity which inhibits fibroblast proliferation and inhibits transforming growth factor-β (TGF-β) induced expression of Type I collagen gene [19]. The most common side effects of 5-FU injection include pain, purpura, transient hyperpigmentation, ulceration, burning sensation, and skin erythema [20].

3-Botulinum toxin:

Botulinum toxin is a potent biological toxin derived from Clostridium botulinum, a gram-positive anaerobic bacterium commonly found on plants, soil, water, and animals’ intestinal tracts. In keloid, BoNT-A inhibits fibroblast proliferation by decreasing transforming growth factor (TGF)-β1 and connective tissue growth factor (CTGF), Also causing downregulations of transforming growth factor (TGF)-β1 gene and upregulation of Matrix metalloproteinase-1 (MMP-1) gene and S100A4 [21]. A combination of triamcinolone acetonide and BTX-A seems to be more effective and has fewer side effects as skin atrophy when compared to each drug alone [22].

4-Bleomycin:

Bleomycin is a cytotoxic antibiotic derived from Streptomyces verticillus. It has antineoplastic, antibacterial, and antiviral properties. It induces fibroblast apoptosis and inhibits lysyl oxidase enzyme and TGF-β1, resulting in collagen reduction. Intralesional bleomycin is given at a dose of 1.5 IU/ml and requires 3–5 sessions to achieve good results in keloid [23]. The most common side

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effects include pain, ulcer, hyperpigmentation, and dermal atrophy. Systemic side effect as pulmonary embolism has not been reported yet [24].

5-Verapamil
Verapamil is a selective calcium channel blocker that blocks the influx of the extracellular matrix calcium into the cytoplasm resulting in activation of procollagenase enzyme and TGF-β1 that cause degradation of keloid tissue. It is given at a dose of 2.5mg intralesional for 6 sessions. The side effect of verapamil injection includes only pain at the injection site [25].

6-Hyaluronidase enzyme:
Hyaluronidase enzyme reversibly depolymerizes the hyaluronic acid into monosaccharides by cleaving its glycosidic bond between C1 of the glucosamine moiety and C4 of glucuronic acid. Also, it breaks down other mucopolysaccharides in the connective tissue [26]. Local injections of hyaluronidase enzyme may cause pain, itching, and allergic reactions as urticaria [27]. Recombinant human hyaluronidase may cause thromboembolism, so it must be used with caution in cardiac patients and hypercoagulable conditions [28]. It can be used in combination with steroids and 5-fluorouracil as triple therapy to manage keloid.

7-Collagenase enzyme:
It acts by degrading collagen, which is the main extracellular matrix component in keloids. The keloid recurrence rate is very high with collagenase injection, so combining with other therapy as compression therapy is advisable. Side effects of collagenase injection include pain, swelling, ulceration, and vesiculation [29].

8- PRP:
Platelet-rich plasma (PRP) is an increased concentration of autologous platelets suspended in a small amount of plasma after centrifugation. It is usually used as adjuvant therapy with TAC injection. It regulates the inflammatory response associated with the healing process via growth factors released after platelet degranulation. These growth factors include platelet-derived growth factors (PDGF-AA, PDGF-BB, PDGF-AB), TGF-β1, TFG-β2, VEGF, and pro-inflammatory cytokines [30].

9- Mitomycin C:
Mitomycin C is an antibiotic produced by Streptomyces caespitosus. It inhibits nucleic acid synthesis, so it inhibits fibroblast proliferation. MMC is used topically or intralesionally to treat keloids with different degrees of success. Intralesional injection of MMC at 1 mg/mL dose causes severe pain and worsens keloid. In contrast, topical application of the same dose for 3 minutes after shaving of keloid shows better results and less pain. So further clinical trials are indicated with different doses of MMC to produce better results [31].

B-Cryotherapy:
It causes keloid tissue microvascular damage, resulting in its necrosis [32]. Different therapies used for cryotherapy include spray and contact probes or intralesional-needle cryoprobe. The intralesional modality is considered superior to other types [33]. Cryotherapy is applied every 2–3 weeks, and better result is achieved when combined with other modalities. Side effects include hypopigmentation, pain, and blistering [34].

C- Laser:

Laser targets skin chromophores as hemoglobin, melanin, and water using the principle of photothermolysis, which causes no damage to the surrounding structures.

Common side effects of laser therapy in keloid treatment include erythema, pain, edema, crusting, hyperpigmentation, hypopigmentation, burns, and infection [35].

1- Pulsed dye lasers (PDLs):

The 585-nm PDL is the most popular laser used in the Treatment of keloids. It destroys the keloid’s capillary leading to hypoxia that stimulates the production of matrix metalloproteinase (MMP) as a collagenase enzyme. It inhibits the expression of TGF-β1 [36]. The recommended energy is 6.0 to 7.5 J/cm2 (7-mm spot) or 4.5 to 5.5 J/cm2 (10-mm spot) [37].

2- Fractional laser

Fractioned CO2 (10 600 nm) and erbium: yttrium–aluminum–garnet (Er: YAG) (2940 nm) deliver energy through columns of microthermal zones (MTZs) that stimulate collagen remodeling and neocollagenesis. Also, they activate MMPs, TGF-β3, and myofibroblasts [38].

3- Long-pulsed 1064 nm Nd: YAG laser

The neodymium-doped yttrium aluminum garnet (Nd: YAG) laser reduces keloid vascularity, decreasing cytokine and growth factors inhibiting abnormal collagen deposition. The recommended energy is 14 J/cm2 (5-mm spot).

Fractional laser is better in firm scars, while Nd: YAG laser is better in erythematous scars [39].

4- Laser-assisted drug delivery (LADD):

The ablative fractional laser promotes transdermal delivery of keloid adjuvant therapy through microthermal zones, allowing equal drug distribution with fewer side effects [40]. Different modalities of LADD are available. Fractional CO2 laser followed by topical application of triamcinolone acetonide 0.1% ointment [41]. Fractional CO2 laser followed by topical application of triamcinolone acetonide suspension (20 mg/mL) or 5-fluorouracil solution (50 mg/mL), which resulted in a reduction in keloid size with 23% with 5-fluorouracil and 27% with triamcinolone acetonide [42].

D- Scar Revision surgery:

Surgical excision of keloid alone is associated with a high recurrence rate of up to 100% [43]. To improve the postoperative surgical outcomes, multimodal combination therapy such as postoperative intralesional injection of steroid, bleomycin, interferon, or radiotherapy must be
done [44]. Most operation includes removing keloid tissue then doing a Z-plasty or flap repair to relieve wound tension [45].

E-Radiotherapy:

It inhibits collagen synthesis by inhibiting angiogenesis and fibroblast activity, thus resulting in cell apoptosis. It is used as adjuvant therapy 24-48h after surgical excision of keloid [46]. Different modalities are available, including electron beam radiotherapy, brachytherapy, and Xray [47]. The recommended dose for keloids on the anterior chest wall is 20 Gray in four fractions over 4 days; for earlobe, keloids are 10 Gray in two fractions over 2 days, and for keloids at other sites, is 15 Gray in three fractions over 3 days [48].

Side effects of radiotherapy include early complications as acute skin reaction that occurs 7 days after radiation, including pain, erythema, edema, ulceration, and desquamations. The late complication occurs several weeks after radiation, including scarring, permanent pigmentation, depigmentation, atrophy, and telangiectasis. Radiotherapy may cause cancer, so it is not recommended for pregnant or radiosensitive sites as breast and genitalia [49]

F-Immunotherapies

1-Interferons:

IFN-γ and IFN-α2b are cytokines with antiproliferative, anti-fibrotic, and antiviral effects ([50]. Both interfere with collagen synthesis and fibroblast proliferation by downregulating TGF-β1. IFN-α2b increases the collagenase enzyme and inhibits the secretion of matrix metalloproteinase (MMPs), a collagenase inhibitor. It is given at a dose of 1.5 million IU twice daily for four days. Better results are obtained when combined with other therapies such as surgical excision, intralesional TAC, and laser. Side effects of IFN therapy include severe pain, erythema, edema, and flu-like symptoms. IFN therapy appears to be a promising therapy in keloid treatment but still needs more clinical trials [51].

2-Imiquimod 5% cream:

Imiquimod is a synthetic imidazoquinolinone amine that has a potent immunomodulatory effect. It stimulates the production of pro-inflammatory cytokines such as TNF-α, interleukins 1,6,8,12, and IFNs. It also alters the expression of apoptotic genes in keloids [48]. It is used daily before or after surgical excision of the keloid for 8 weeks. The rate of keloid recurrence in patients who have received imiquimod cream after surgical excision was 24.7%. Side effects of imiquimod cream include pain, erosion, erythema, and edema at the site of application [52]

3-Tacrolimus:

Tacrolimus is a calcineurin inhibitor with potent immunosuppressive effects in atopic dermatitis. It inhibits T cell activation, inhibiting fibroblast migration, proliferation, and collagen production. Further clinical trials of its application are required [48]
4- Transforming growth factor-β:

Several isoforms of TGF-β are available (e.g., TGF-β1, -β2, and -β3). TGF-β3 has anti-fibrotic properties, while TGF-β1 and TGF-β2 increase fibrosis. Avoteren is a recombinant human TGF-β3 used intralesionally in keloids with good and promising results and minimal side effects as erythema and edema [53]

G- Stem cell therapy:

Mesenchymal stem cells (MSC) are multipotent stromal cells that can differentiate into various cell types and show immunomodulatory and anti-fibrotic effects [54]. MSC stimulates modulation of macrophage and T-cell function, neutralizing reactive oxygen species, producing anti-fibrotic factors, angiogenesis, and collagen remodeling. It can be injected, topically applied, or grafted. More trials are required [55].

H- Angiotensin-converting enzyme inhibitor:

ACEI is an antihypertensive drug used in the Treatment of keloid by inhibiting the expression of Ang II, which is elevated in keloid patients, TGF-β1 and proliferation of fibroblast and collagen synthesis. It can be taken orally as enalapril or applied topically as captopril cream (5%) [56].

I- Tamoxifen:

Tamoxifen is a selective estrogen receptor modulator (SERMs) used in the Treatment of cancer breast. In keloid, it inhibits TGF-β1 and proliferation of fibroblast. Tamoxifen citrate 0.1% is applied topically in keloid with good results [57].

Reference:


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