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Review Article

Keloids: clinical features and management. Part I

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Abstract Keloids are benign tumours of fibrous origin which clinical ly present as firm, fesh-coloured tumours. The exact etiology is not known; nevertheless, there have been many associated dermatoses. Therapeutically, keloids have been a challenging disease and not a single effective therapy is available. The present review presents the clinical features and therapeutic update of this common malady.

Key words
Keloid, hypertrophic scars, clinical features, management.

Introduction

Keloids are benign, well-demarcated tumours of fibrous tissue overgrowth that extend beyond the original defect. These are characterized by firm, mildly tender, bosselated tumours occurring more frequently on shoulders, chest, neck, upper arms and cheeks. The consequent cosmetic disfigurement often leads to psychogenic turmoil and severe depression.[1]

Keloids occur in all age groups although mainly in the third decade of life. Both sexes are equally affected. The disease is more common in blacks as compared to whites.[2] Keloidal scars are commonly found in Asian and African populations.[3]

The etiology of keloids is unknown but a number of precipitating factors e.g. surgery, tattoos, bites, vaccination, blunt trauma, burns and lobular piercing. They may occur spontaneously or may be familial.[2,3] Similarly, many other dermatological diseases are associated with keloid formation. Various treatment modalities with variable success have been reported which include compression therapy, intralesional steroids, cryotherapy, surgical excision, radiation, interferons, 5-fluorouracil, bleomycin, silicon gel, UV-A_1 therapy, methotrexate, Quercetin and laser therapy.[4,5,6,7]

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Historical background

There are different hypotheses about the origin of the word keloid. According to one hypothesis, it is derived from the Greek word "Chele" meaning crab's claw [3].

Retz described the lesion as "dartre de graisse" meaning fatty hernia in his book "Treatise on Skin Diseases and Things of Mind" published in 1790, probably a misnomer since the clinical description was suggestive of keloid.[3] The earliest recorded reference to keloids is in the Smith Papyrus (3000-2500 BC) who described "the existence of swellings on his chest, large, spreading and hard.[3] Cultural studies of ancient

Yoruba people of Eastern Nigeria have disclosed that they were practising ritual facial marking and recorded characteristics of the keloid diathesis in their oral and sculptural art forms of the 10th century A.D.[3]

in 1825 described keloids as true when arising spontaneously and false keloid when arising at sites of trauma. Addison in 1854, described as "true keloids" the lesions which we now know as morphea or scleroderma.[3]

Epidemiology

Incidence

Keloids and hypertrophic scars affect 4.5% to 16% of general population.[3,4,5] First estimate of the frequency of keloidal scars in black patients compared with white patients was calculated by Matas.[4] Keloidal scars occur 3 to 18 times less in white patients than in blacks. The true incidence remains unknown. Most researchers agree that keloidal scars occur in all races but more common in black patients.[3,4]

Age of onset

Keloids can develop at any age but most cases occur between 10 and 30 years of age.[4]

Sex incidence

Keloids occur equally in both sexes.[3,4,5]

Hereditary influence

Both autosomal recessive and autosomal dominant inheretance patterns have been reported. A positive family history is more likely in cases of multiple, severe keloid formation.[3,4]

Precipitating factors

The documented precipitating factors are surgery, lacerations, tattoos, burns, injection sites, bites, vaccination, piercing and blunt trauma. Another risk factor is presence of foreign material either exogenous (e.g. suture material) or endogenous (e.g. embedded hair). Persons with blood group A also have an increased tendency to develop keloid. Some African tribes introduce foreign bodies into tribal marks to induce scar hypertrophy. Scarring acne on trunk may become keloid like.[5,6]

Isotretinoin has been reported to delay wound healing and induce keloids in patients who received argon laser or dermabrasion for acne or rosacea. Linear keloids can occur in athletes taking anabolic steroids.[7,8]

Clinical presentation

Keloids appear as firm, mildly tender or pruritic, bosselated, well-demarcated tumours occurring more frequently on shoulders, chest, neck, upper arms, earlobes and cheeks. Keloids are variable in size from 2 to 3 mm papules to large pendulous tumours. Shapes vary from evenly contoured symmetric protrusions with regular margins to irregular clawlike projections. The colour of keloid is also variable, mildly erythematous in new lesions while dull red or more pale in older lesions. Keloids may occur on eyelids, genitalia, palms, soles, cornea or mucous membranes rarely.[1,2,3]

Keloids develop rapidly over weeks or months following trauma or other precipitating factors. The lesions may continue to grow or remain stable for long periods of time. Sometimes, keloids may undergo central suppurative necrosis. This change is thought to be due to ischaemic necrosis from vascular compromise secondary to keloid overgrowth. Dark skinned individuals are more susceptible to keloid formation, especially on the face. Growth of keloid may be stimulated by pregnancy.

Surgically resected keloid is followed by regrowth of a larger tumour and if skin graft has been used, keloid may occur in donor site as well.[3,4]

Differences between hypertrophic scars and keloidal scars

Clinical

Keloidal scar is a lesion that persists for more than 12 months. It extends beyond the original wound and spreads by invasion rather than expansion. These scars can occur in other animal species besides human beings i.e. horses, cows and dogs.[4] Small injury may produce a large lesion. They are independent of areas of motion and worsened by surgery. Areas of high predilection are chest, shoulders, back, earlobes, neck etc. The disease is likely to recur.

Hypertrophic scar is a lesion that may regress with time and occur earlier after injury and limited to the boundary and are more responsive to surgical excision. Its size is directly proportional to that of injury. They occur in areas of motion and occur across flexor surfaces like joints and abdomen.

Some researchers have suggested that because the keloids and hypertrophic scars are so similar, they should be considered together while others have the opinion that the different behaviour of these scars invalidates this approach.[5]

Light microscopy

On light microscopy, keloidal scars reveal large collagen bundles but they are not seen in hypertrophic scars. Keloids have few macrophages but numerous eosinophils, mast cells, plasma cells and lymphocytes. Keloids are associated with mucopolysaccharide ground substance. No morphological differences in keloidal and hypertrophic scar fibroblasts have been found but their biologic effect is different.[5,6]

Hypertrophic scars have nodules containing cells and collagen within the mid-to deep part of scar. Within these nodules, there are α-smooth muscle actin staining myofibroblasts which are absent from normal dermis, normal scars and keloidal scars.[7]

Electron microscopy

There are amorphous substances found around the keloidal fibroblasts which separate them from the collagen bundles. This is not seen in hypertrophic scars. Collagen bundles are crisp in hypertrophic scars while glazed in keloidal scars. Differences are found in the degree of microvascular injury which is seen in the keloidal scars.[7,8,9]

Metabolic activity

Keloidal scars have higher levels of adenosine triphosphate and fibroblasts than hypertrophic scars. There is a higher density of fibroblasts in both types of scars but keloidal scars have a higher expression of proliferating cell nuclear antigen this may explain the tendency of keloidal scars to grow beyond the boundary of the original injury or trauma.[10,11,12]

Other differences

Antinuclear antibodies against fibroblasts, epithelial and endothelial cells have been found in patients with keloidal scars but not in hypertrophic scars.[12]

Pathology

Normal wound healing and keloid formation share same histopathologic appearances in early

stages. Both have an early inflammatory stage followed by fibroplasia which has an increased vascularity and a moderate perivascular mononuclear infiltrate along with early production of proteoglycan and collagen fibers and bundles. Cellular infiltrate is characterized by a number of mast cells, plasma cells and lymphocytes. In keloid formation, fibroplasia progresses and fails to peak by 3rd week of wound healing time.

Nodular vascular proliferation along with fibroblasts enlarges and transforms into thickened nodular mass of collagen and proteoglycan. This persistent transformation of swir-like fibroblast clusters into hyalinized collagen bundles appears essential for keloid growth.[12] In hypertrophic or mature wound healing, the number of fibroblasts and capillaries slowly decreases by 5th week as more organized collagen becomes parallel.

The collagen fibers and bundles in normal skin or mature wounds lie parallel to the epithelial surfaces in discrete groups. In keloids, the organization of collagen bundles and fibers is more haphazard. Discrete bundles are absent and collagen fibers are loosely connected in sheets with random orientation with respect to epithelial surface.[3,12]

It has been suggested that high levels of nitric oxide may lead to excessive collagen secretion by fibroblasts and results in keloid scars.[13]

In keloid, collagen types I and III, messenger RNA levels are found to be up-regulated twenty-fold and HSP 47 is also highly up regulated.[14]

Pathogenesis

Keloids are more cellular than normal dermis. Fibroblasts of keloids demonstrate enhanced metabolic activity which is reflected by increased activity of glycolytic enzymes and an increased synthesis of glycoproteins. In spite of this hyperplasia and increased metabolic activity, growth characteristics of fibroblasts from keloids are similar to those of normal dermal fibroblasts.[15]

Keloid-derived fibroblasts synthesize type-I procollagen and fibronectin at a greater rate than fibroblasts derived from normal dermis.[15,16] Normal dermal fibroblast growth is stimulated by epidermal growth factor which can be reversed by transforming growth factor β_1. Transforming growth factor β_1 can also stimulate keloid fibroblast proliferation in response to epidermal growth factor. Major sources of transforming growth factor β_1 are platelets, macrophages, fibroblasts and smooth muscle cells. Transforming growth factor β_1 can also enhance the expression of several collagen types by fibroblasts. Due to this, it plays an important role in the development of fibrotic diseases such as keloid.[16]

Interleukin-1 induces the expression of adhesion molecules and stimulates chemotaxis and activation of neutrophils and lymphocytic cells. Its activity in skin is associated with epidermal cells but it is now clear that dermal fibroblasts are induced by interleukin-1. These are essential activities during the repair phase of wound healing and in the induction of fibrosis. Growth factors such as platelet-derived growth factor and epidermal growth factor induce fibroblast migration and proliferation.[17]

In keloids, mast cells are prominent which release histamine. Increased histamine level may explain pruritus complained by patients of

keloids. Mast cells are also abundant in healing wounds and histamine formation is linked to wound healing.[18]

The abundance of extracellular material is responsible for most of the tumescence of keloids. Proteoglycan content and accompanying water are increased. Much of the proteoglycan in keloid is chondroitin-4-sulphate which is associated with active nodular areas in keloids.[19,20,21]

Collagens synthesis is increased in keloid tissue. The activity of prolyl-hydroxylase enzyme is increased which reflects collagen synthesis.[22,23] Amount of collagen synthesis is dependent on the age of the keloid, early keloids have more abundant collagen synthesis.[24] Nature of collagen synthesized appears to differ from that of normal dermis relative amounts of type III collagen are increased.[25] The amount of type III collagen depends upon variables e.g. duration of keloid and sampling area. Keloid collagen is more soluble than dermal collagen and the profile of reducible collagen intermolecular cross linking remains more like that of young skin collagen.[19,26] Collagen cross-linking depends on lysyl oxidase, a copper dependent enzyme, reduced copper levels in keloids may be important in abnormal cross-linking.[26]

The accumulation of fibrous tissue found in keloids results from altered degradation. Collagenase activity in keloids is found to be normal or increased but not diminished.[27] Collagenase activity is inhibited by α_2-macroglobulin and α_1-antitrypsin.

Immunofluorescence studies have revealed accumulation of these substances in keloids.[28,29] Corticosteroid treatment appears to diminish this tissue deposition. Collagen synthesis is decreased by glucocorticoids which may result in enhanced collagen breakdown in keloids.[30]

Characteristics of keloid

A. ***Increased cellularity***
   1. More cells histologically
   2. Increased DNA content
   3. Increased metabolic activity

B. ***Abnormal proteoglycan content***
   1. Increased proteoglycan content
   2. Increased water content
   3. Marked increase in chondroitin-4-sulphate content

C. ***Abnormal collagen synthesis***
   1. Increased collagen synthesis in tissue and keloid fibroblasts
   2. Increased type-III collagen synthesis
   3. Increased soluble collagen
   4. Immature collagen cross-link profile

D. ***Abnormal collagen degradation***
   1. Increased collagenase content
   2. Increased content of α_1-antitrypsin and α_2-macroglobulin

Differential diagnosis

Keloids can be differentiated from hypertrophic scars, as described earlier. Hypertrophic scars remain within the boundary of initial injury. They are not claw-like and often regress spontaneously.

Keloids can be distinguished histologically from dermatofibrosarcoma protuberans, clinical picture of which may be similar to keloids.[31]

Allergic contact dermatitis secondary to gold earrings may produce keloidal lesions on the earlobes but histopathologic study of these lesions shows a dense infiltration of

Table 1 Disorders occurring more frequently with keloids [32].

1. Acne conglobata
2. Acne vulgaris
3. Hidradenitis suppurativa
4. Pilonidal cysts
5. Foreign body reaction
6. Local infection with herpes, smallpox or vaccinia
7. Pseudofolliculitis barbae
8. Dissecting cellulitis of the scalp
9. Pregnancy
10. Dupuytren's contracture
11. Acromegaly
12. Thyroidectomy in young patients
13. Pachydermoperiostosis
14. Dubowitz syndrome (case report)
15. Ehlers Danlos syndrome
16. Rubinstein-Taybi syndrome
17. Turner's syndrome
18. Noonan's syndrome
19. Facial dysmorphism gingival hyperplasia (FG syndrome)

lymphocytes and formation of lymphoid follicles rather than dense collagen tissue.[32]

Keloids can be differentiated from lobomycosis (keloidal blastomycosis). In lobomycosis, on histopathology there are abundant fungi and giant cells in the lesions which are granulomatous and devoid of collagenous fibrosis.[2,8]

Association of keloids with other conditions

Keloids are associated with many conditions as shown in **Table 1**.

Work up of a patient of keloid

Diagnosis is usually based on clinical findings. Biopsy helps confirm the diagnosis in case of uncertainty.

Prognosis

Keloids rarely resolve spontaneously. Patients often present for cosmetic reasons. These lesions are often uncomfortable. Malignant degeneration of keloids is reported in very few documented cases.

References

1. Burton JL, Lovell CR. Disorders of connective tissue. In: Champion RH, Burton JL, Burns DA, Breathnach SM, eds. *Textbook of Dermatology*. Oxford: Blackwell Science; 1998. p. 2003-71.
2. From L, Assaad D. Neoplasms, pseudoneoplasms and hyperplasias of the dermis. In Freedberg IM, Eisen AZ, Wolff K *et al*., eds. *Dermatology in General Medicine*. New York: McGraw-Hill; 1999. p. 1161-75.
3. Child FJ, Fuller LC, Higging EM, Vivier DU. A study of the spectrum of skin disease occurring in a black population in South-East London. *Br J Dermatol* 1999; **141**: 512-7.
4. Shaffer JJ, Taylor SC, Cook-Bolden F. Keloidal scars: a review with a critical look at theratpeutic options. *J Am Acad Dermatol* 2002; **46**: 63-97.
5. Kuflik EG. Cryosurgery updated. *J Am Acad Dermatol* 1994; **31**: 925-44.
6. Ragoowansi R, Paul GS, Glees JP. Treatment of keloids by surgical excision and immediate postoperative single-fraction radiotherapy. *Plast Rec Sur* 2003; **111**: 1853-9.
7. Granstein RD, Rook A, Thomas J, Amento EP. A controlled trial of intralesional recombinant interferon-γ in the treatment of keloidal scarring. *Arch Dermatol* 1990; **126**: 1295-1302.
8. Graham FG. Cryosurgery. In: Freedberg IM, Eisen AZ, Wolff K *et al*., eds. *Dermatology in General Medicine*. New York: McGraw-Hill; 1999. p. 2980-7.
9. Layton AM, Yip T, Cunliffe WJ. A comparison of intralesional triamcinolone and cryosurgery in the treatment of acne keloids. *Br J Dermatol* 1994; **130**: 498-501.
10. Dawber R, Colves G, Jackson A, eds. *Cutaneous Cryosurgery*. London: Martin Dunitz; 1997.

11. Brody GS. Keloids and hypertrophic scars. *Plast Reconstr Surg* 1990; **86**: 804.
12. Heenan PJ. Tumors of the fibrous tissue involving the skin. In Elder D, Elenitsas R, Jaworsky C, Johnson B, eds. *Lever's Histopathology of the Skin*. New York: Lipincott-Raven; 1997. p. 847-87.
13. Cobbold CA. The role of nitric oxide in the formation of keloid and hypertrophic lesions. *Med Hypotheses* 2001; **57**: 497-502.
14. Naitoh M, Hosokawa N, Kubota H *et al*. Upregulation of HSP47 and collagen type III in the dermal firbotic disease, keloid. *Biochem Biophys Res Commun* 2001; **280**: 1316-22.
15. Luo S, Benathan M, Raffoul W *et al.* Abnormal balance between proliferation and apoptotic cell death in firboblasts derived from keloid lesions. *Plast Recon Sur* 2001; **107**: 87-96.
16. Rodland KD, Muldoon LL, Magun BE. Cellular mechanisms of TGF-β action. *J Invest Dermatol* 1990; **94**: 33S-40S.
17. Heckmann M, Grill BCA, Hein R, Kriegs T. Biphasic effects of interleukin-1α on dermal fibroblasts: enhancement of chemotactic responsiveness at low concentrations and of mRNA expression for collagenase at high concentrations. *J Invest Dermatol* 1993; **100**: 780-4.
18. Hebda PA, Collins MA, Tharp MD. Mast cell and myofibroblast in wound healing. *Dermatol Clin* 1993; **11**: 685-96.
19. Garner WL, Karmiol S, Rodriguez JL *et al*. Phenotypic difference in cytokine responsiveness of hypertrophic scar versus normal dermal fibroblasts. *J Invest Dermatol* 1993; **101**: 875-9.
20. Lim IJ, Phan TT, Bay BH *et al.* Fibroblasts co-cultured with keloid keratinocytes: normal fibroblasts secrete collagen in a keloid like manner. *Am J Physiol Cell Physiol* 2002; **283**: C212-22.
21. Meyer LJM, Stern R. Age dependent changes of hyaluronan in human skin. *J Invest Dermatol* 1994; **102**: 385-9.
22. Murray JC. Scars and keloid. *Dermatol Clin* 1993; **11**: 697-708.
23. Tuan TL, Huayang WU, Eunice Y *et al*. Increased plasminogen activator inhibitor-1 in keloid fibroblasts may account for their elevated collagen accumulation in fibrin gel cultures. *Am J Pathol* 2003; 162: 1579-89.
24. Peltonen J, Hsiao LL, Jaakkola S *et al*. Activation of collagen gene expression in keloids: co-localization of type-I and VI collagen and transforming growth factor β1 mRNA. *J Invest Dermatol* 1991; **97**: 240-8.
25. Richard AFC, Denver CO. Cutaneous tissue repair. Basic biologic consideration. *Am Acad Dermatol* 1985; **13**: 710-25.
26. Pettinger DA, Yager DR, Diegelmann RF, Cohen IK. The effect of TGF-β on keloid fibroblast proliferation and collagen synthesis. *Plast Reconr Surg* 1996; **98**: 827-33.
27. Glat PM, Longaker MT. Wound healing. In: Aston SJ, Beasley RW, Thome CHM. *Grabb and Smith's Plastic Surgery*, *5th edn.* Philadelphia: Lippincott-Raven; 1997. p. 3-12.
28. Lim IJ, Phan TT, Tan WTL, Longaker MT. Investigation of the influence of keloid-derived keratinocytes on fibroblast growth and proliferation in vitro. *Plast Recon Surg* 2001; **107**: 797-808.
29. Datubo-Brown DD. Keloids: a review of the literature. *Br J Plast Surg* 1990; **43**: 70-7.
30. Tsao SS, Dover JS, Arndt KA, Kaminer MS. Scar management: Keloid, hypertrophic, atrophic and acne scars. *Semin Cutan Med Surg* 2002; **21**: 46-75.
31. Niessen FB, Spaumen PH, Schalkwij KJ *et al*. On the nature of hypertrophic scars and keloids: a review *Plast Recon Sur*g 1999; **104**: 1435-58.
32. Gold MH. A controlled clinical trial of topical silicone gel sheeting in the treatment of hypertrophic scars and keloids. *J Am Acad Dermatol* 1994; **30**: 56-7.