Keloid or Hypertrophic Scar

The Controversy: Review of the Literature

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Abstract: Keloid and hypertrophic scars are 2 types of excessive scarring observed clinically that require different therapeutic approaches. The clinical course and physical appearance define keloids and hypertrophic scars as separate entities; however, they are often confused because of an apparent lack of morphologic differences. Nevertheless, clinical differences between hypertrophic scars and keloids have long been recognized by plastic surgeons and dermatologists. Yet, translating these differences into morphologic or biochemical distinctions has prompted much conflict in the literature. The present report is an attempt to clarify the longstanding controversy regarding these 2 similar yet separate and nonidentical entities by highlighting the reported points of differentiation as well as the similarities.

Key Words: keloid, hypertrophic scar, cutaneous scar, dermal tumor

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Cutaneous scars are one of the most frequently encountered conditions.[1] The process of wound repair and restructuring is complicated, and various factors contribute to the creation of various types of scars such as hypertrophic, atrophic, or normotrophic.[1] Regulation of connective tissue formation during development and repair processes is under the rigorous control of a number of soluble mediators acting in concert to ensure tissue integrity and homeostasis.[2–4] Structural proteins and glycoproteins must be deposited and removed at appropriate rates to ensure a healthy, functional scar.[5] Disruption of the fragile equilibrium between anabolic and catabolic cytokines may lead to extracellular matrix synthesis and deposition.[2–4] A regional skin susceptibility to excessive scarring affecting certain parts of the body, such as the earlobes and sternum, is also a well-documented and recognized fact.[6–8] Hypertrophic scars and keloids are 2 forms of excessive dermal fibrosis and cutaneous scarring[9] thought to be caused by some kind of disorder in the regulation of cellularity increase and decrease during the wound-healing process.[1,5,10] Both keloid and hypertrophic scars can be viewed as dermal tumors that are often familial and typically occur in certain races. The incidence of keloid scars has been estimated at 4.5% to 16% in the black and Hispanic populations in several large series, and the incidence of hypertrophic scarring is certainly greater than that.[11] Their exact etiopathogenesis continues to remain an enigma.[6]

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Clinical and Morphologic Differentiation

Keloids are fibrous overgrowths at sites of cutaneous injury that form as a result of an abnormal wound-healing process in genetically susceptible individuals[12,13] and, unlike normal scars, do not regress.[6,14,15] Keloid disease is a benign dermal fibroproliferative tumor unique to humans[6,14–16] that never becomes malignant.[17] Although its exact cause is still unknown, it is thought that the condition is due to a failure to turn off the healing process. Extra collagen forms at the site of the scar and continues to form,[17] extending beyond the confines of the original wound.[14–18] Some authors reported that keloid-derived fibroblasts seem to function autonomously and produce increased amounts of collagen per cell compared with normal fibroblasts in culture.[2,19] A hypertrophic scar, on the other hand, also appears to be raised above the skin level; however, it is distinct from a keloid in that it stays within the confines of the initial wound and increases in size by pushing out the margins of the scar, not by invasion of surrounding normal tissue.[5,6] Scar-classification schemes, nevertheless, include the 2 conditions as various degrees of scarring in a continuum ranging from mature scar, immature scar, linear hypertrophic scar, widespread hypertrophic scar, to minor keloid and major keloid.[20]

Clinical differences between hypertrophic scars and keloids have long been recognized by plastic surgeons and dermatologists. Yet, translating these differences into morphologic or biochemical distinctions has prompted much

conflict in the literature.[21] Attempts have been made to distinguish hypertrophic scars from keloids and find an efficient diagnostic method.[22] Differentiating the 2 conditions, however, can be problematic.[20] Though the differences are real, they are in no way overwhelming.[15] Both conditions have a similar prevalence in male and female gender and have the highest incidence in the second decade.[6] They tend to occur in all races; however, keloid disease is reported to occur more often in dark-skinned individuals.[5,6,7,16] Contrary to hypertrophic scars, keloids do not regress with time, are difficult to revise surgically, and do not provoke scar contractures.[23] Major keloids are a most challenging clinical problem, and many are resistant to any treatment.[20] As opposed to keloid disease, hypertrophic scars often can undergo resolution over a period of time.[6] Surgical excision of hypertrophic scars or keloids is a common management option when used in combination with steroids and/or silicone gel sheeting. However, excision alone of keloids results in a high rate of recurrence (45% to 100%).[20] Hypertrophic scars, on the other hand, rarely recur after surgical excision.[6]

Of the various risk factors implicated pathologically, none has proved significant pathogenetically.[8,14] Nevertheless, one element in the etiology of keloid disease clearly stands out, namely, its familial nature.[7,24] There is, however, a familial predisposition in both keloid disease and hypertrophic scars, although more cases of keloid disease have been reported to have a familial tendency.[6] It was proposed that the likely mode of inheritance in keloid disease is autosomal recessive. It is, however, unclear whether keloid disease is a complex oligogenic condition or a simple monogenic Mendelian disorder.[6] So far, no genetic study has been able to detect a gene or genes involved in keloid disease pathogenesis.[6,24]

Histopathologic Differentiation

Differences between keloids, hypertrophic scars, and normal scars include distinct scar appearance, histologic morphology, and cellular function in response to growth factors.[14] Distinguishing hypertrophic scar from keloid histopathologically is undoubtedly sometimes very difficult as the 2 conditions may look almost identical.[1,25] Keloids and hypertrophic scars differ from normal skin and normal scars by their rich vasculature, high mesenchymal cell density, inflammatory-cell infiltration, and thickened epidermal cell layer.[1,26] Both lesions have a predominant active fibroblast cell type, but keloids tend to have more quiescent forms.[21] Though hypertrophic scars and keloids have a distinct pattern of vascularization compared with normal skin and normal scars, no differences can be observed in the pattern of vascularization of hypertrophic scars and keloids.[26] Both show high levels of occluded microvessels[21]; however, comparison of numbers and magnitude of several organelles of endothelial cells suggests keloids may be more similar to mature scars than to hypertrophic scars.[21] In both conditions, collagen fibers are organized in swirls. Few macrophages are present, while some lymphocytes and eosinophils exist.[15] Keloids contain large, thick collagen fibers composed of numerous fibrils closely packed together. In contrast, hypertrophic scars exhibit nodular structures in which fibroblastic cells, small vessels, and fine, randomly organized collagen fibers are present. Such nodular structures are always present in hypertrophic scars and rarely in keloids.[23]

Histologic criteria characteristic of keloids but not of hypertrophic scar include the presence of broad eosinophilic refractile hyaline-like collagen fibers.[15,27,28] Thickened hyalinized collagen (keloidal collagen), the hallmark of keloid is, however, not always detectable. Keloidal collagen is only found in 55% of keloid specimens. α-Smooth muscle actin, a differentiating marker of hypertrophic scars, is variably expressed in both forms of scar and is found in both hypertrophic scars (70%) and keloids (45%); thus, it would not be a differentiating marker.[25] The features more commonly seen in keloids are (a) no flattening of the overlying epidermis, (b) no scarring of the papillary dermis, (c) presence of keloidal collagen, (d) absence of prominent vertically oriented blood vessels, (e) presence of prominent disarray of fibrous fascicles/nodules, (f) presence of a tonguelike advancing edge underneath normal-appearing epidermis and papillary dermis, (g) horizontal cellular fibrous band in the upper reticular dermis, and (h) prominent fascia-like fibrous band. The last 3 features are found in keloid specimens only, including the ones lacking detectable keloidal collagen.[25] In scars with no detectable keloidal collagen, the presence of the following features favors the diagnosis of keloid: nonflattened epidermis, nonfibrotic papillary dermis, a tonguelike advancing edge, horizontal cellular fibrous band in the upper reticular dermis, and prominent fascia-like band.[25]

The use of light microscopy to distinguish keloids from hypertrophic scars remains difficult, but the scanning electron microscope demonstrates distinct morphologic differences.[15] Normal skin contains distinct collagen bundles, the majority of which run parallel to the epithelial surface. Collagen weave in hypertrophic scars is decisively different from that in normal skin or mature scar. Collagen bundles are flatter and less clearly demarcated, loosely arrayed in a wavy pattern, fragmented, and shortened, but the majority of bundles lies parallel to the epithelial surface. The ultrastructure of keloids shows even less organization.[15] Their collagen fibrils are larger and more irregular, and the interfibrillar distance is less than that in hypertrophic scars.[21] Discrete collagen bundles are virtually nonexistent, and the fibers lie in haphazardly connected, loose sheets that appear randomly oriented to the epithelial surface. Higher magnification confirms the random nature of fiber orientation, varying fiber length, and poor bundle formation.[15]

Thick sections of keloid tissues stained with Toluidine Blue O show a glazing of the collagen bundles, whereas they are crisp in hypertrophic scars. When examined by transmission electron microscopy, the collagen fibrils of keloids in the glazed areas were larger, more irregular, and the interfibrillar distance is less than in hypertrophic scars. The occurrence of the irregular fibrils in keloids may reflect a significant difference in terms of collagen synthesis, fusion, or breakdown. It is also suggested that the essential difference between keloids and hypertrophic scars may be in the volume of microvessels injured, and, hence, the amount regenerated, the number of pericytes, fibroblasts, and, consequently, the amount of collagen synthesized.[21]

Molecular Biology Differentiation

Findings support the hypothesis that cell-mediated, major histocompatibility complex class II–restricted immune responses play an important role in the development of both hypertrophic scars and keloids.[29] Nevertheless, morphophenotypic differences between keloids and hypertrophic scars have been determined in Caucasians. Contrary to hypertrophic scars, the histologic profile of keloids is not related to the age of the lesion.[29] Ultrastructurally, myofibroblasts are the predominant cell type in young and fully developed hypertrophic scars and in keloids. The immune-cell infiltrate in both conditions is composed of CD3+, CD45RO+, $CD4^+$, human lymphocyte antigen (HLA)-DR+, and lymphocyte function associated antigen-1+ T lymphocytes, strictly associated with CD1a+/CD36+, HLA-DR+, and intercellular adhesion molecule-1+ dendritic cells. However, in hypertrophic scars, different amounts of immune cells are observed in relation to the type and age of the lesion.[29]

A study of extracellular matrix elements and of elastic system components (fibrillin-1 and elastin) demonstrated that the distribution of fibrillin-1 and elastin is disrupted in all kinds of scars, but 2 patterns can be clearly defined: one for normal scars and another for excessive pathologic scars.[9] When hypertrophic scars are compared with keloids, no differences in the fibrillin-1 volume density are determined in the superficial and deep dermis.[9] Elastin volume density in the superficial dermis is usually higher in normal skin than in hypertrophic scars or keloids. In the deep dermis, however, the elastin volume density is higher in keloids compared with normal skin, normal scars, as well as hypertrophic scars.[9]

Immunohistochemistry employed to detect the expression and distribution of fatty acid synthase (FAS) protein demonstrates that the expression level of FAS antigen is much higher in keloids and their surrounding normal skins than in hypertrophic scars. No significant difference in the expression level between the keloids and their surrounding normal skins can be observed. In hypertrophic scars, however, much lower FAS protein expression can be detected in comparison with that in their surrounding normal skins ($P <$ 0.01). Immunohistochemical detection of FAS protein is a simple method that could well be applicable in the differential diagnosis to distinguish the 2 forms of pathologic scars.[22]

It is now accepted that apoptosis, or programmed cell death, plays a pivotal role during embryogenesis, tissue remodeling, and cell turnover.[17] Recent studies suggest that the regulation of apoptosis during wound healing is important in scar establishment and development of pathologic scarring[1,17,30] and that this type of scarring may result from alterations in genes that would normally induce apoptosis.[17,31] In fact, regulation of apoptosis and proliferation of fibroblasts is altered in keloids in which the rate of collagen synthesis continues to be higher than that in normal scar.[1] Keloid-derived fibroblasts show a lower rate of apoptosis than normal fibroblasts.[17,32] p53, p63, And p73 genes play distinct and overlapping roles in apoptosis and subsequently in scar formation and development of unfavorable scars.[1] In scars with various clinical manifestations, the expression of p53 varies and seems to be related to scar maturation. The more active phase, the higher is the level of p53 expression.[1] Though the kinetics of p53 gene expression in keloid and hypertrophic scar formation has not been clearly identified, the level of p53 is significantly highest in keloids, underlying the significant difference between keloids and hypertrophic scars.[1,17] The role of p53 may also differ between hypertrophic scars and keloids, which have characteristics similar to tumors, such as a tendency to grow beyond the site of original injury without spontaneous regression.[1] p53 Gene mutation has been reported in keloids, resulting in a nonfunctional weak expression and lack of cellular apoptosis.[1,17,33] p63 Immunohistochemical analysis, on the other hand, shows that in human normal skin it is virtually undetectable. Only the basal cells of the epithelium express the protein. In contrast, human keloid tissues show strong p63 expression not only in basal cells but throughout the suprabasal layer of epithelial cells, in the dermis and around dermal blood vessels.[17] Increased expression of ΔNp63 in keloids is consistent with the aberrant growth seen in these tissues and suggests that aberrant p63 expression may underlie neoplastic and proliferative potential.[17] It has also been suggested that p63 could serve as aspecific molecular keloid marker.[17]

Immunohistochemical staining of caspase-3, normally activated during apoptosis, is significantly higher for the combination of hypertrophic scars and keloid as a group compared with normally healed flat scars, suggesting reduced cell survival and increased apoptotic cell death in hypertrophic scars and keloid.[30] In contrast to hypertrophic scar-derived and normal skin-derived fibroblasts, keloid-derived fibroblasts are significantly resistant to both FAS-mediated and staurosporine-induced apoptosis.[34] The resistance can be overcome by the addition of transforming growth factor (TGF)-β2.[34] This important observation clearly demonstrates that it is becoming more and more important to recognize the

differences and treat keloids as a separate entity different from hypertrophic scars. Enhancement of FAS-sensitivity could be a promising therapeutic target.[34]

Hypertrophic scar fibroblasts show a consistently higher basal level of fibrin matrix gel (FMG) contraction than other fibroblasts.[35] Fibroblasts isolated from different scars, however, exhibit varied degrees of FMG contraction. Hypertrophic scar fibroblasts showed a consistently higher basal level of FMG contraction than other fibroblasts. Normal and keloid fibroblasts exhibited similar basal rates of FMG contraction, and both responded to platelet-derived growth factor (PDGF) and TGF-β by increasing FMG contraction 2- to 3-fold. However, 45% of the TGF-β-induced increase in FMG contraction by keloid fibroblasts, but not normal fibroblasts, was mediated by the autocrine production of PDGF.[35] There are also major differences in the proteoglycans (PG) composition of scar tissues between keloids and hypertrophic scars. Higher proportions of low-density chondroitin sulfate proteoglycans (CS-PGs) are present in the keloid scars only, while low-density dermatan sulfate proteoglycans (DS-PGs) can be detected in both hypertrophic and keloid scars.[36] Moreover, the observed invasive growth of keloid may be related to the overexpression of angiogenesis factors and their receptors. The abnormal expression of 11B5 (vascular endothelial growth factor/KDR complex) in keloid myofibroblasts may be one of the important factors associated with tumorlike growth feature in the invasive sites of keloid.[37] Moreover, epidermal keratinocytes of keloid seem to play an important role in keloid pathogenesis through paracrine epithelial-mesenchymal signaling.[1,38]

CONCLUSION

There are 2 types of excessive scarring observed clinically: keloid and hypertrophic scars. These 2 lesions require different therapeutic approaches but are often confused because of an apparent lack of morphologic differences.[23] In fact, the clinical course and physical appearance define keloids and hypertrophic scars as separate entities.[16] Several morphologic and immunohistochemical differences exist between the 2 conditions that are useful for the biologic and pathologic characterization of the 2 lesions. It is becoming more and more important to recognize these differences and treat keloids as a separate entity different from hypertrophic scars.[34] Understanding the genetic basis of keloid disease and hypertrophic scars may provide future prognostic and diagnostic advice to patients and may help to develop novel therapeutic regimens for the treatment of the various forms of skin fibrosis.[6]

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