

## **Keloid and Hypertrophic Scars: Comparative Histopathological and Immunohistochemical Study**

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*Abstract.* Keloids and hypertrophic scars are different expressions of the same derailment of wound healing; their biological behaviors and appearances are quite different. The clinical differences between hypertrophic scars and keloids have long been recognized. However, distinguishing between the two types of scars on histology is sometimes difficult as the 'keloid collagen', the hallmark of keloid, is not always present. Plus the  $\alpha$ -smooth muscle actins, a differentiating marker of hypertrophic scar is variably expressed in both forms of scars. The present study is an attempt to reinforce the validity of existing criteria and to investigate additional distinguishing features to facilitate the distinction between these two entities. The morphological features and the expression of  $\alpha$ -smooth muscle actins in myofibroblasts in the two conditions have been investigated. These results demonstrate that keloids are characterized by the presence of collagen fibers, which are abnormally large, dense, broad, glassy, eosinophilic, focally fragmented complexes, arranged haphazardly and packed together by "keloid collagen". In contrast hypertrophic scars exhibit collagen, which is discretely nodular, fibrillar with fairly regular thickness of fibers with its long axis parallel to the epidermis. It was confirmed that such nodular structures are always present in hypertrophic scar and rarely in keloid. Furthermore, keloid scars occasionally show myofibroblasts expressing  $\alpha$ -smooth muscle actins, while hypertrophic scars are negative for  $\alpha$ -smooth muscle actins.

*Keywords:* Keloid, Hypertrophic scars, Histopathology,  $\alpha$ -SMA.

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## Introduction

Hypertrophic scars and keloids are macroscopic cutaneous scarring caused as the result of disturbance of wound healing, which occurs on predisposed individuals. It shows a kind of over-healing, producing over abundant wound matrix responsible for raised, red, inflexible scar tissue, which causes itching and pain. It can also lead to serious functional and cosmetic concerns<sup>[1-5]</sup>. Excessive scarring following trauma that creates tissue loss is identified into two types; hypertrophic scars and keloid scars.

The first is known as hypertrophic scars, and they remain confined to the boundaries of the original lesion, generally regressing spontaneously after the initial injury. They may produce scar contractures *e.g.*, when located over joints. Most hypertrophic scars do not recur after surgical excision.

The second type of excessive scarring that develops from either a deep or a superficial injury is known as a keloid scar. Keloids are also red and itchy. Thus, they exceed the boundaries of the initial injury as they do not regress with time, or with high recurrent rate after surgical excision, and usually they do not provoke contractures<sup>[1,2,4]</sup>.

Individuals of all ethnic backgrounds can form keloid and hypertrophic scars as a familial predisposition was believed to exist. Keloid formation is approximately 15 times greater in highly pigmented ethnic groups than in whites. The pathogenesis of keloid scar is complex which involves both genetic and environmental factors<sup>[2,6]</sup>. Distinguishing hypertrophic scar from keloid histopathologically may present a diagnostic challenge. Several methods and techniques are used to investigate the features of both entities in order to facilitate their differentiation. Histopathological studies and immunohistochemical studies are among the most extensively applied criteria.

Histopathological differences between keloid and hypertrophic scar have been reported using hematoxylin and eosin stain. Among these differences, keloid scar is characterized by the presence of thick, hyalinized collagen bundles or 'keloid collagen' with mucinous ground substance and relatively few fibroblasts. Conversely, little or no keloidal collagen is found in hypertrophic scar. A histopathological characteristic of hypertrophic scar is the presence of nodules containing a high density

of cells and collagen. The collagen fibers are cigar-shaped and run parallel to the surface of the skin. They are located in the middle or deeper layer of the scar, and are oriented along the tension lines of the scar. The absence of such nodules is characteristic of keloid scars. Hypertrophic scars have numerous fibroblasts but few glassy collagen bundles and scanty mucinous ground substance. Collagen fibers in the ordinary and hypertrophic scars are oriented parallel to the long axis of the scar, whereas in keloid, collagen is arranged in a haphazard pattern<sup>[3,4,7-9]</sup>.

The objective of this study is to investigate the morphological features in depth; the possible biologically and diagnostically relevant differences between keloid and hypertrophic scar using histopathological and immunohistochemical studies. The organization of collagen fibers was determined by hematoxylin and eosin stained sections. The presence or absence of myofibroblasts was demonstrated by  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA) immunostaining. Such distinctive features may help in understanding the pathogenesis of these lesions; their differentiation and interpretation of the clinical behavior. Furthermore, planning the management since keloid is more difficult to treat and is highly recurrent with frustrating management.

### **Material and Methods**

This study was conducted as part of a research project to study the abnormal scars in patient treated in the plastic surgery unit at King Abdulaziz University Hospital (KAUH). Thirty-five samples of hypertrophic, keloid and normal scars were collected and sorted based on clinical diagnosis obtained from the record of patients. Samples were taken from excised skin scars during patient's management, the Ethics and Research Committee approved this study as fulfilling the ethical requirements. Written consent was obtained from patients before operative excision of scars.

#### ***Histopathological Study with Light Microscope***

Formalin fixed, paraffin embedded tissue sections were stained with hematoxylin and eosin, and examined in detail under a light microscope. The following histological and histopathological features of each parameter, with the variable findings, were used to evaluate and

differentiate the scars as normal, hypertrophic or as a keloid scar. The parameters and their variable findings are:

- Epidermis (normal finding or flattened or hyperplastic)
- Epidermal features associated (hyper parakeratosis or hypergranulosis or spongiosis)
- Basal cell organization (regular palliate or disarray)
- Basal cell vacuolar change (present or absent)
- Papillary dermis (normal or scarring)
- Collagen site (papillary or reticular dermis)
- Collagen arrangement (haphazard, nodules or parallel to the skin surface)
- Collagen quality (large, broad hyalinized or fibrillar, regular or wavy)
- Collagen cellularity (Myofibroblasts: numerous, scant or acellular)
- Horizontal fibrous bands in upper reticular dermis (prominent or inconspicuous)
- Advancing edge underneath epidermis (present or absent)
- Myxoid extracellular matrix (present or absent)
- Orientation of blood vessels (horizontal, vertical or aggregating)
- Inflammatory infiltrate (mild or moderate and its location)
- Mast cells (present or absent)

### ***Immunohistochemical Study***

Immunohistochemical staining using an automated stainer with the avidin-biotin-peroxidase complex method was performed using the antibody  $\alpha$ -SMA (dilution 1:50 Dako, Carpinteria, CA, USA). Results were scored as follows:

- (-) not seen.
- (+/-) rare/focal positivity.
- (+) diffuse positivity.

Positive and negative controls were performed for the stain. However, since  $\alpha$ -SMA always stains the vessels, it was used as an internal positive control. Each of the histopathological parameters were evaluated and graded with a qualitative score of present or absent.

The presence or absence of myofibroblasts was demonstrated by  $\alpha$ -SMA immunostaining in normal scar, keloid and hypertrophic scar.

The diagnosis of keloid was based on the clinical characteristics, among which extension of the scar beyond the original wound and growth in mounds over mounds were the most definitive diagnostic features. In those cases where these features were uncertain, the diagnosis was supported by history of the lesion progressively enlarging for long duration (more than 6 months) and post excision recurrence. Cases which fell short of these considerations were excluded from the study. Presence of advancing front was recorded as positive or negative in the specimens, where the scar border was visible in the sections. The diagnosis of hypertrophic scar was based on the clinical characteristics among which the most definitive feature was the lesion remaining confined to the boundaries of the original wound with history of regression spontaneously after the initial injury. A scar was considered as normal when injury healed without becoming red, raised, or rigid when compared to a normal skin.

## Results

Detailed histopathological examination of the keloid, hypertrophic and normal scars revealed various morphologic features; results are summarized in Tables 1, 2 and 3.

**Table 1. Histopathological features seen on light microscopy in the epidermis.**

Histopathological Features	Normal Scars N = 10	Hypertrophic Scars N = 10	Keloid Scars N = 15
<b>Epidermis</b>			
Normal thickness with rete ridges	2		10
Normal thickness with flattening	4	10	5
Hyperplastic	4		
<b>Epidermal features associated</b>			
Hyperkeratosis	10	10	15
Hypergranulosis	10	10	15
Spongiosis	3	3	14
<b>Basal cell organization</b>			
Regular palliating	9	1	13
Disarray	1	9	2
<b>Basal cell vacuolar change</b>			
Present	3	2	14
Absent	7	8	1

**Table 2. Histopathological features seen on light microscopy in the dermis.**

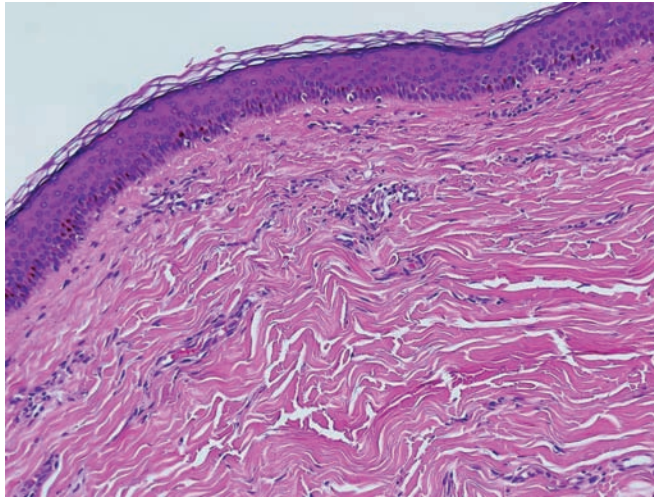
Histopathological Features	Normal Scars N = 10	Hypertrophic Scars N = 10	Keloid Scars N = 15
<b>Papillary dermis</b>			
Normal	1		1
Scarring	9	10	14
<b>Collagen site</b>			
	10 (Papillary dermis & upper half of reticular)	10 (Papillary dermis & upper one third of reticular)	15 (Papillary dermis & full thickness of reticular)
<b>Collagen arrangement and quality</b>			
Haphazard			15 (large, broad, glassy, eosinophilic focally fragmented complexes)
Nodules		10 (fibrillar & of fairly regular thickness)	
Parallel to skin	10	10	
Wavy	10 (delicate)		
<b>Collagen cellularity</b>			
Acellular			5
Myofibroblasts			
Numerous		10	10
Rare	10		
<b>Horizontal fibrous bands in upper reticular dermis</b>			
Prominent			14
Absent	10 (absent)	10 (absent)	1 (inconspicuous)
<b>Advancing edge underneath epidermis</b>			
Present			12
Absent	10	10	3
<b>Myxoid extracellular matrix</b>			
Present			10
Absent	10	10	5
<b>Orientation of blood vessels</b>			
	10 (horizontally)	10 (vertically oriented around the nodules)	15 (aggregating below the epidermis with in or out growth)
<b>Chronic inflammatory infiltrate</b>			
Mild			
Moderate	10	2	
Location			15
Mast cells	2	3	11

**Table 3.  $\alpha$ -SMA expression in fibroblastic cells of connective tissues.**

Scale	Tissue	$\alpha$ -SMA expression*		
		-	+/-	+
Normal scar	n = 10		+/-	
Hypertrophic scar	n = 10	- (in all)		
Keloid	n = 15	- (in 10)		+ (in 5)

Scale: - = not seen; +/- = rare focal positivity; + = diffuse positivity.

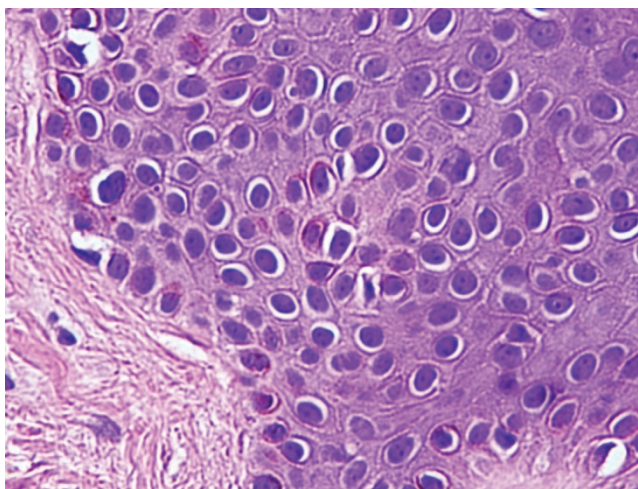
\* Vascular walls are always labeled for  $\alpha$ -SMA



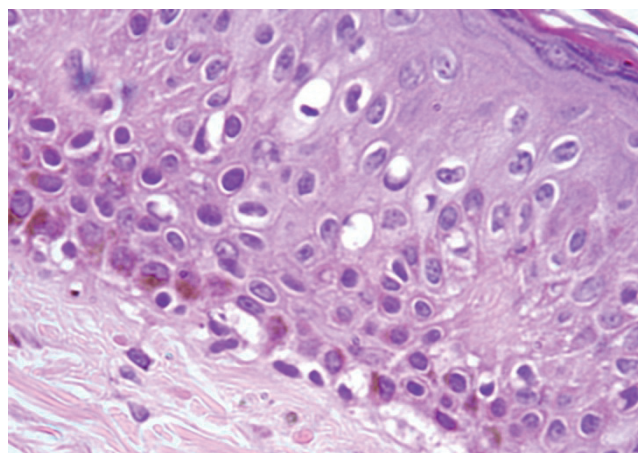
**Fig. 1. Hypertrophic scar 20 X showing epidermal flattening with scarring of papillary dermis and horizontally oriented wavy collagen fibers.**

Epidermal changes was illustrated in Table 1 as follows: Flattening of epidermis was more prominent in hypertrophic scars (100%) (Fig. 1) and was only seen in 33.33% of keloid scars. Hyperkeratosis and hypergranulosis were consistent features in all types of keloid scars, hypertrophic scars and normal scars. Spongiosis is mostly apparent in 93.33% of keloid scars, while it was only seen in 30% of each of hypertrophic and normal scars (Table 1). Basal cell organization was regular and palliating in keloid scars (86.66%), whereas hypertrophic scar showed disarray in 90% (Fig. 2). Basal cell disarray seen in hypertrophic scars correlated with the obliteration of the rete ridges and discrete flattening of the epidermis seen in all of these cases. Basal cell vacuolar change was diffusely prominent in the keloid scars (93.33%) (Fig. 3), but less common in hypertrophic scars (20%) and normal scars (30%). The presence of basal cell vacuolar change in the keloid group

correlated with the added presence of spongiosis in all of these cases. Scarring of papillary dermis was very prominent in all hypertrophic scars (100%) and frequent in keloid scars (93.33%) and normal scars (90%).



**Fig. 2. Hypertrophic scar 40X showing epidermal disarray.**

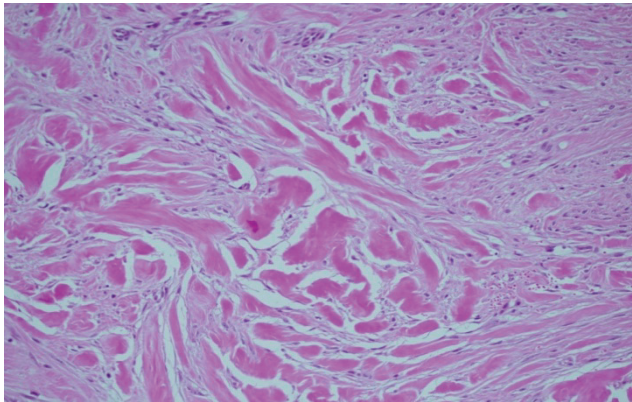


**Fig. 3. Keloid scar 40 X showing basal cell vacuolar change.**

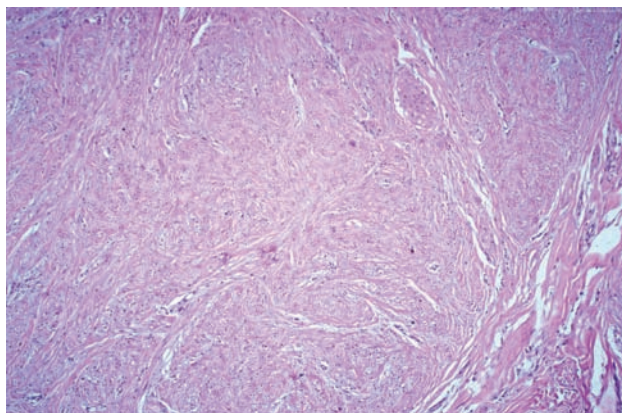
The dermal changes was illustrated in detail in Table 2 as follows: The collagen was seen spanning full thickness of the dermis including the papillary dermis in all keloid scars (100%), while it remained confined to the upper one third of reticular dermis in all hypertrophic scars (100%). The normal scars collagen was confined to the upper half of the reticular



dermis. The collagen quality in all keloid scars (100%) was that of abnormally large dense, broad, glassy, eosinophilic, focally fragmented complexes, arranged haphazardly (Fig. 4). These complex collagen bundles were shown to be associated with variable amounts of "extracellular myxoid matrix" in (86.66%) keloid scars. On the other hand, the collagen in all hypertrophic scars (100%) was discretely nodular, fibrillar with fairly regular fiber thickness having their long axis parallel to the epidermis with no extracellular myxoid matrix (Fig. 5).

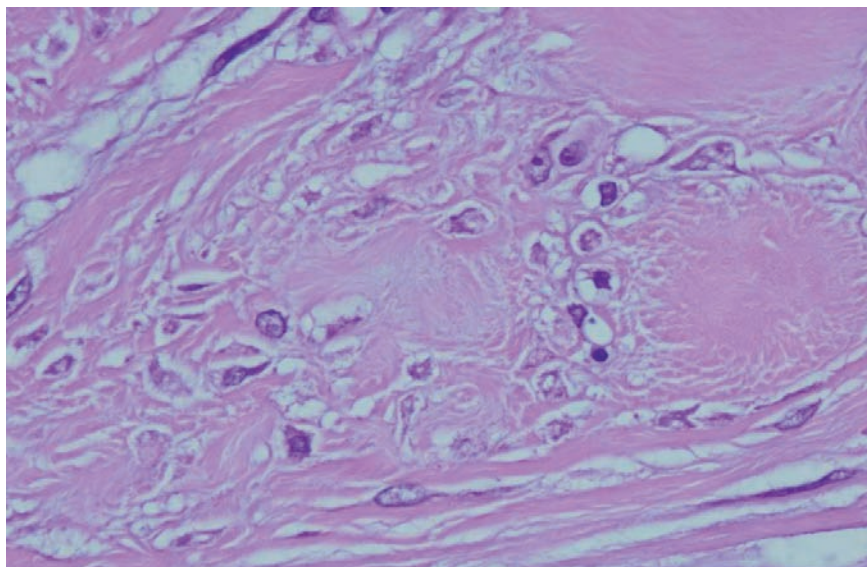


**Fig. 4.** Keloid scar 40 X showing abnormally large dense, broad, glassy, eosinophilic, focally fragmented complexes, arranged haphazardly.

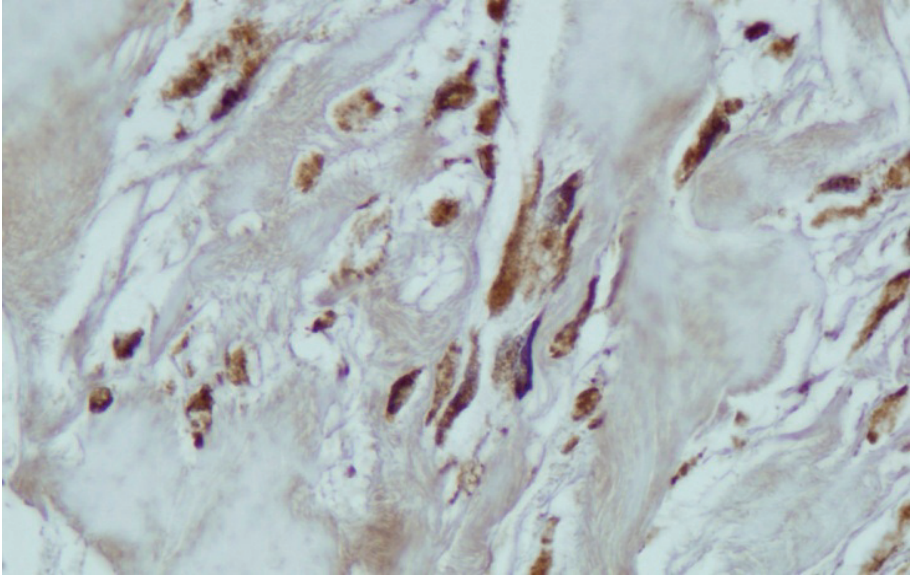


**Fig. 5.** Hypertrophic scar 40 X showing nodules of fibrillary collagen of fairly regular thickness.

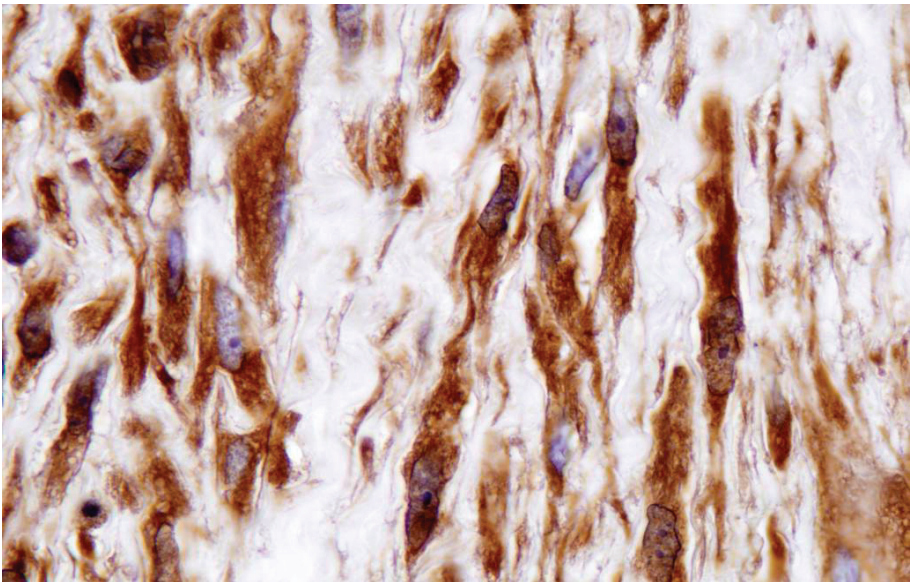
The collagen in normal scars (100%) was wavy, delicate and parallel to the long axis with no extracellular myxoid matrix. The collagen was cellular in (66.66%) keloid scars and in (100%) hypertrophic scars. Rare cellularity was a feature of normal scars. Presence of cellularity was correlated only to a small extent with the expression of  $\alpha$ -SMA by these cells; positive  $\alpha$ -SMA indicates that the cells were myofibroblasts (Table 3). Diffused positive  $\alpha$ -SMA was seen only in (33.33%) keloid scars (Fig. 6: a, b, c), while all hypertrophic scars (100%) failed to show expression of  $\alpha$ -SMA (Fig. 7). Collagen in the nodules of hypertrophic scar were generally oriented parallel to each other. Horizontal fibrous bands in the upper reticular dermis were prominent in (93.33%) keloid scars (Fig. 4) and were absent in all (100%) of the hypertrophic and normal scars. An advancing edge below the epidermis was present in (66.66%) keloid scars (Fig. 8), and was absent in all hypertrophic and normal scars. Blood vessels were seen aggregating below the epidermis in all keloid scars (100%) with a tendency of growing towards or from the epidermis, were vertically oriented around the nodules in all (100%) the hypertrophic scars as compared to the horizontal orientation in all (100%) normal scars. Chronic inflammatory infiltrate was of moderate degree in all (100%) keloid scars and was perivascular in location; scattered mast cells were seen in (73.33%) (Fig. 9).



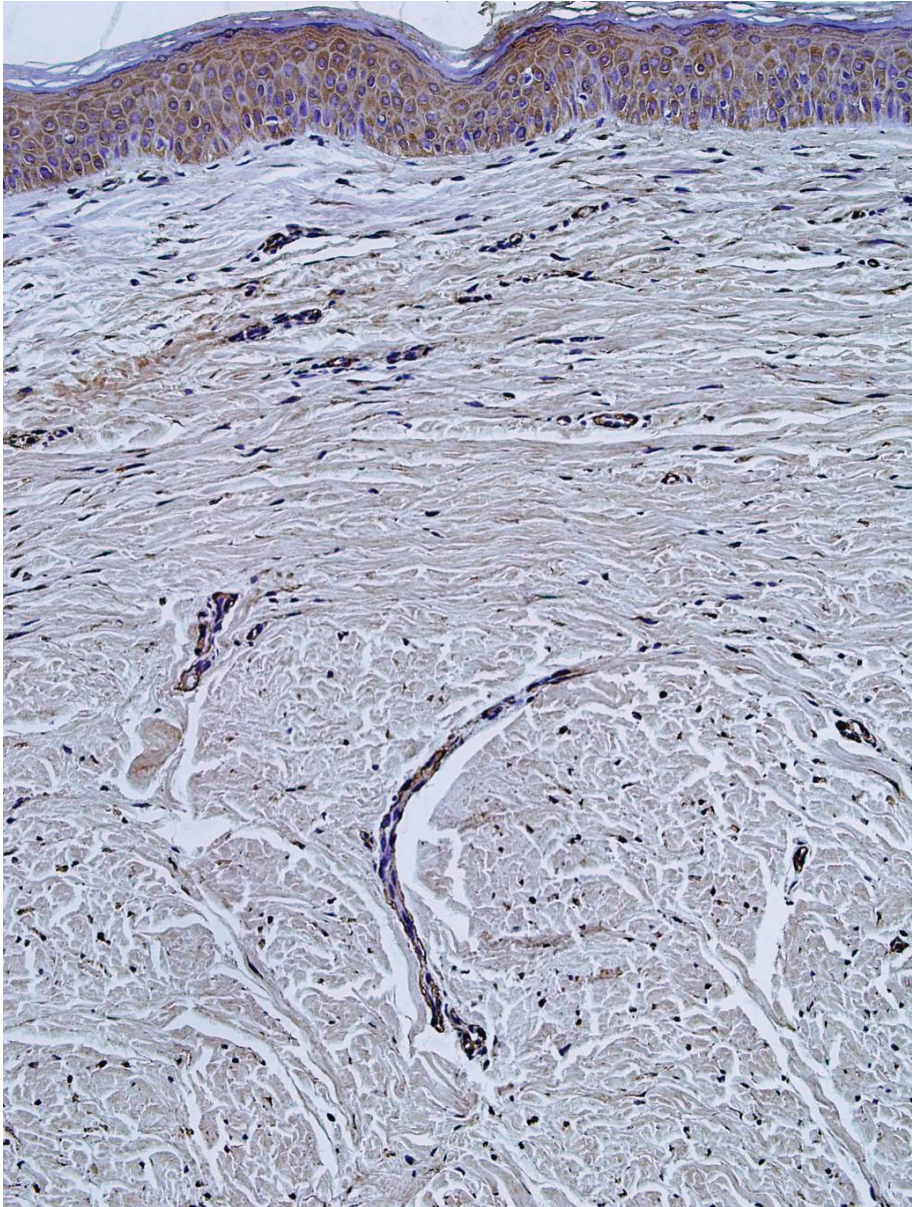
**Fig. 6(a). Keloid scar 40 X showing broad glassy collagen.**



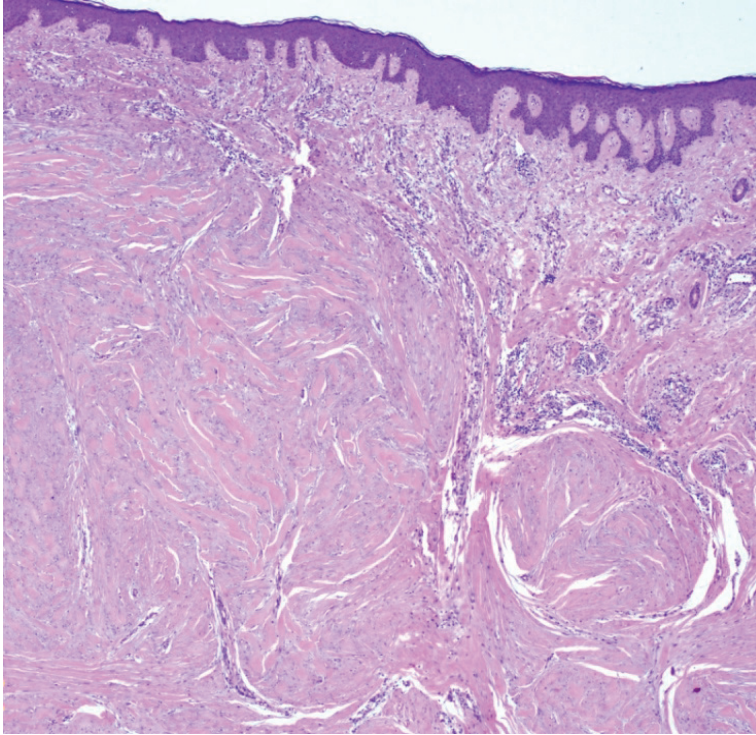
**Fig. 6(b).** Keloid scar 60 X showing  $\alpha$ -SMA expressing myofibroblasts with glassy collagen.



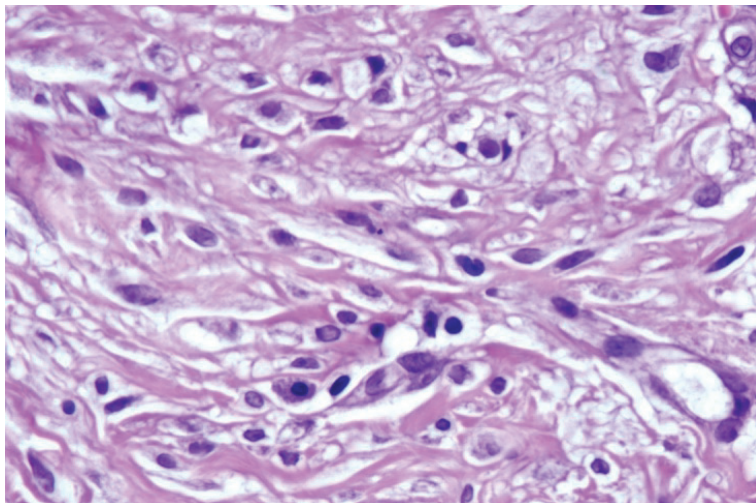
**Fig. 6(c).** Keloid scar 40 X showing diffuse positivity for  $\alpha$ -SMA expressing myofibroblasts.



**Fig. 7.** Hypertrophic scar 40 X showing absence of  $\alpha$ -SMA expressing myofibroblasts. Note vertical blood vessels at the margins of collagen nodules.



**Fig. 8.** Keloid scar 20 X showing advancing edge below the epidermis.



**Fig. 9.** Keloid scar 40 X showing chronic inflammatory infiltrate and mast cell.

Hypertrophic scars showed mild perivascular chronic inflammatory infiltrate in 20%, with scattered mast cells confined to the reticular dermis and occasionally around blood vessels in 30%. Normal scars showed mild chronic inflammatory infiltrate in all 100%, with scattered mast cells in 20%.

### Discussion

While there was little disagreement about distinctions concerning the gross appearance of keloid and hypertrophic scars, histopathological differences between them are often considered to be insignificant. There are conflicting reports in literature as to whether there are histopathological distinctions between these two scars. These results confirm and extend the reports of histopathological differences between keloid and hypertrophic scars, these are:

1) The first difference was in the epidermal features; the keloid scars demonstrated normal thickness of epidermis in all cases with regular and palliating basal cell organization, and basal cell vacuolar change in most cases. The papillary dermis show scarring in many keloid scars. On the other hand, the epidermis in all hypertrophic scars was flattened, with disarray of basal cells in most cases and vacuolar change in few. These epidermal changes of keloid scars are concordant to other studies in literature, and are suggestive of presence of prior external injury to the dermis locally. This correlates well with the fact that keloid scarring develops from either a deep or a superficial injury. In contrast, some studies report epidermal hyperplasia in keloid, and this could be explained partly, by the phenotypic variations in the study groups<sup>[3,4,8,10,11]</sup>.

2) The second difference was the collagen quality and orientation of the scar; all keloid scars in our study demonstrated the presence of large, broad, glassy, eosinophilic focally fragmented and haphazardly arranged collagen complexes referred to as “keloid collagen” in association with variable amounts of myxoid extracellular matrix in most cases. As opposed to hypertrophic scar which showed nodules containing fibrillar collagen of fairly regular thickness arranged parallel to the epidermis, with absence of myxoid extracellular matrix with high density of cells. Similar differentiating findings are reported in other studies<sup>[3,4,12,13]</sup>.

Verhaegen *et al.* found that compared with normal skin, normotrophic scar, and hypertrophic scar, the bundle distance was significantly larger in keloid scar, which confirms that thicker collagen bundles are present in keloid scar<sup>[14]</sup>. Abnormally, large collagen bundle complexes associated with variable amounts of "ground substance" mucopolysaccharides have been identified in keloid scar, but are absent from hypertrophic scars. This was explained by the fact that compared to normal dermal fibroblasts keloid, fibroblasts exhibit increased production of collagen and matrix metalloproteinase. Additionally, the keloid collagen occupied full thickness of the reticular dermis in all cases, while remained confined to the upper one third in the hypertrophic scars. This again correlates with the exuberant amount of collagen and extension beyond boundaries of actual wounds in the keloid scar<sup>[4,12,13]</sup>.

3) The third difference was that "keloid collagen" showed positivity for  $\alpha$ -SMA expressing myofibroblasts in only one third of keloid scars while the collagen nodules of hypertrophic scars contained no  $\alpha$ -SMA expressing myofibroblasts, although they were cellular. There are wide variations in the literature regarding  $\alpha$ -SMA expression in scars ranging from completely negative in keloid to 45% keloid cases positive, and the same for hypertrophic scar, 70% positive to most cases in another study<sup>[3,15]</sup>.

Possible explanations for this variation between different studies are: (a) Differences in genetic backgrounds of the population studied (b) differences in the criteria used for diagnosing scars, positivity scales used for  $\alpha$ -SMA expression; (c) presence of mixed keloid - hypertrophic scars in the sample populations studied (d) interobserver variability.

Histopathological characteristic of hypertrophic scar has the presence of nodules containing a high density of cells and collagen similar in appearance to the nodules described in Dupuytren's contracture. They are cigar-shaped and run parallel to the surface of the skin, are located in the middle or deeper layer of the scar, plus they are oriented along the tension lines of the scar. The absence of such nodules is characteristic of keloid scar. Myofibroblasts are differentiated fibroblasts found in granulation tissue and fibrotic lesions. They differ from normal fibroblasts by their characteristic cytoplasmic bundles of microfilaments, nuclear indentations and cell-to-cell or cell-to-stroma connections. Moreover, a large proportion of myofibroblasts express smooth muscle

proteins such as  $\alpha$ -SMA and desmin. It was well accepted that myofibroblasts appear temporarily in granulation tissue during wound healing, but are present permanently in hypertrophic scars and other fibrotic settings<sup>[4,16-18]</sup>.

4) The fourth difference was the presence of horizontal fibrous bands in all keloid scars with an advancing edge underneath the epidermis in 66% of cases, and the total absence of such features in all the hypertrophic scars. Similarly, these features have been reported in other studies. Some authors describe this phenomenon as “pseudopodia-like extensions” into the surrounding tissue<sup>[3,8]</sup>.

5) The fifth difference was the presence of small aggregating blood vessels just below the epidermis appearing to grow out or from it, in the keloid scars, while in the hypertrophic scars the blood vessels were oriented vertically around the nodules. Prominent telangiectasia in the papillary dermis has been reported in keloid scars and vertically oriented blood vessels have been reported in the hypertrophic scars. The evidence demonstrates that hypertrophic scars and keloids are hypoxic, undoubtedly due to the microvascular occlusion. Hypoxia may stimulate excessive production of collagen, which forms the bulk of these lesions, from fibroblasts and myofibroblasts<sup>[3,7,19]</sup>.

6) The sixth difference was in the presence of moderate degree of perivascular chronic inflammatory infiltrate in all keloid scars, with mast cells seen in the reticular dermis in 73%, as compared to hypertrophic scars where this feature was seen infrequent in 20-30% of cases. Immunohistochemical investigations have shown a high amount of activated immune-cell infiltrate in the excised keloid scars, consisting of CD3+, CD4+, CD45R0<sup>[20,21]</sup>.

Several studies investigated the contribution of lymphocytes and macrophages to keloid scarring by morphologically characterizing inflammatory cell subpopulations in keloid scars. It was found that there was a significantly higher CD4 (+):CD8(+)(Th:Ts) ratio in keloid tissue, suggesting that an imbalance in these inflammatory cell subpopulations may contribute to keloid scarring mast cells in the middle dermis as they are activated and may be involved in the pathogenesis of keloid scars<sup>[22,23]</sup>.



## Conclusion

This report confirmed the diagnostic value of keloid collagen in all of the keloid scars in this present study group. Other features which favor the diagnosis of keloid scar are the scarring of papillary dermis, presence of horizontal fibrous bands and advancing front below the epidermis. Presence of horizontal blood vessels just below the epidermis, presence of moderate degree of perivascular chronic inflammatory infiltrate with mast cells and variable  $\alpha$ -SMA expression in the lesional myofibroblasts. On the other hand, it does confirm that hypertrophic scars diagnostic value includes cellular collagen nodules with vertically oriented vessels at the nodule margins and absence of  $\alpha$ -SMA expressing myofibroblasts. This present study indicates that  $\alpha$ -SMA expression is variably seen in keloid scars suggesting that this feature could not reliably help in distinguishing the two types of scars and that pathogenesis of keloid scars is multifactorial and refutes the clonal theory of origin. This was supported by a study of the morphology and biochemistry of keloid scars by Knapp *et al.* who demonstrated multiple phenotypic differences in cells derived from keloid scars<sup>[6,24]</sup>. Such distinctive features may help in understanding the pathogenesis of these lesions, their differentiation, interpretation of the clinical behavior and planning the appropriate management of abnormal scar and avoid its recurrence.

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## الجدرة والندبة الجلدية: دراسة مقارنة باستخدام الدراسات النسجية وكيمياء الأنسجة المناعية

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المستخلص. تعتبر الجدرة والندبة الجلدية وصفان تعبيريان لشكلين من خلل في التئام الجروح، ويتباين المظهر والتغيرات البيولوجية بين الجدرة والندبة الجلدية. ومن المعروف أن هنالك فروقاً واضحة في الصفات الإكلينيكية بين الجدرة والندبة، أما الفروق في التركيب النسيجي فقد تكون صعبة، حيث أن الدراسات النسيجية للجدرة تظهر زيادة ترسيب الألياف الكولاجينية السميقة التي تميز الجدرة عن الندبة، وهي الصفة الغالبة في التركيب النسيجي للجدرة التي قد لا تظهر في بعض الحالات. أما بالنسبة للندبة، فهي تتميز بوجود أكتين العضلات الرقيقة أ، وحتى هذه الخاصية تتفاوت في وجود الصفات الظاهرة التعبير للأكتين في الخلايا الليفية النشطة في كل من الندبة والجدرة. تضمنت الدراسة الحالية محاولة إثبات فعالية المواصفات المتعارف عليها للتفريق بين الحالتين، والفوارق الإضافية للتفريق بينهما. ولقد تم فحص الصفات الظاهرة التعبير للأكتين في الخلايا الليفية النشطة في كل من الحالتين. وقد أظهرت النتائج أن الجدرة تتميز بزيادة في ترسيب الألياف الكولاجينية، وهي عبارة عن كتل كبيرة سميقة ومتجانسة بؤرية وداكنة

الاصطبغ بالإيوسين الوردى، تتجزأ وتترتب في شكل عشوائي يسمى (كولاجين الجدره). أما بالنسبة للندبة تتميز بوجود الكولاجين على شكل عقد منتشرة وألياف خيطية مقبولة السمك ومنظمة بحيث يكون محورها الطولي موازي للبشرة. ولقد أثبتت الدراسة أن تلك العقد توجد في كل حالات الندبات، ونادراً ما توجد في الجدره. بالإضافة إلى أن الصفات الظاهرة التعبير للأكتين في الخلايا الليفية النشطة تظهر أحياناً في الجدره ولا تظهر أبداً في الندبات.