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ORIGINAL ARTICLE

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Keloids and hypertrophic scars of Caucasians show distinctive morphologic and immunophenotypic profiles

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Abstract The aim of this study was to identify possible morpho-phenotypic differences between keloids (K) and hypertrophic scars (HS) in a Caucasian population. Young HS (≤1 year of age) presented a high number of diffusely distributed spindle-shaped cells (α-smooth-muscle actin$^+$ and fibronectin$^+$). Fully developed HS (>1 year of age and <3 years of age) were characterized by the frequent presence of distinct collagenous cellular nodules (cells: α-smooth-muscle actin$^+$ and fibronectin$^+$). Old HS (≥3 years of age) showed widespread collagenization phenomena. The histological profile of K was not related to the age of the lesion and was characterized by the almost constant presence of abnormally thick, hyalinized collagen fibers, the presence of collagenous cellular nodules, and variable – albeit lower than in HS – expression of α-smooth-muscle actin and fibronectin. Ultrastructurally, myofibroblasts were the predominant cell type in young and fully developed HS and in K. The immune-cell infiltrate was composed of CD3$^+$, CD45RO$^+$, CD4$^+$, human lymphocyte antigen (HLA)-DR$^+$, and lymphocyte function associated antigen (LFA)-1$^+$ T lymphocytes, strictly associated with CD1a$^+$/CD36$^+$, HLA-DR$^+$, and intercellular adhesion molecule (ICAM)-1$^+$ dendritic cells, both in HS and K. However, different amounts of immune cells were observed in relation to the type and age of the lesion, and these findings support the hypothesis that cell-mediated, major histocompatibility complex (MHC)-class II-restricted immune responses play an important role in the development of HS and K.

Keywords Hypertrophic scars · Keloids · Caucasian race · Histology · Immunohistochemistry

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Introduction

Keloids (K) and hypertrophic scars (HS) result from an abnormal wound healing process. Keloids were first described in the Smith papyrus and later by Retz [28] in 1790 and by Alibert [2] in 1806, who proposed the current name derived from the Greek $\chi\eta\lambda\eta$ (kelé), meaning claw, and $\varepsilon\iota\delta\eta\zeta$ (eidés), meaning resembling. Keloids are defined as raised pathologic scars that grow beyond the limits of the original wound and, in contrast, HS are raised scars that remain within the boundaries of the wound [7, 23, 27, 29]. Keloids generally persist for many years, often cause pruritus, itching or pain and rarely regress, whereas HS frequently regress spontaneously. Keloids occur in all races, with a preponderance of the disease in Africans [24]. More darkly pigmented tribes are particularly prone to K formation and develop more prominent scars than Caucasians [1, 17]. Caucasians and albinos are the least affected [1, 7, 17, 23, 24]. The use of light microscopy to distinguish HS from K has remained difficult. HS and K differ from normal skin and normal scars by their rich vasculature and high mesenchymal cell density; collagen fibers are organized in swirls [12, 29]. It has been reported that HS are characterized by the presence of nodules containing a high density of cells and collagen [4, 11] and K are characterized by hyalinized collagen bundles [4, 14]. The collagen isoforms present in HS and K are similar, some differences having been demonstrated in the ratio of collagen I and III [7, 23] and in procollagen mRNA levels studied by means of in situ hybridization [23, 31, 32]. It has also been shown that HS are characterized by the presence of

α-smooth-muscle actin (α-SMA) positive myofibroblasts in the nodular structures, which are absent in typical K of patients of African origin [9]. However, some authors describe whorls and nodules both in HS and K and the presence of the highly eosinophilic staining bands in both types of scars [12, 19, 20, 22].

In order to complement previous studies, we have investigated these pathologic scars in a Caucasian population using histological, immunohistochemical, and ultrastructural techniques. The lesions were classified as HS or K applying strict clinical criteria and were compared according to their age. This investigation extends the observation of histological and immunohistochemical differences between HS and K, reveals differences among HS according to their age, and indicates that K in Caucasians may be different from those in Africans.

Materials and methods

Study population

In this study, we included scars that presented typical clinical features of HS (raised scars within the boundaries of the original wound) or K (raised scars invading the surrounding skin; Fig. 1) [7, 23, 27, 29]. We excluded from the study those lesions where it was not possible to evaluate precisely whether or not the pathologic scar tissue had invaded the normal skin surrounding the original wound. Scars treated with any therapy were also excluded from the study.

A total of 54 patients of both sexes was recruited for the investigation; 28 patients had HS (17 females and 11 males, aging from 16 years to 63 years) and 26 patients had K (14 females and 12 males, aging from 10 years to 54 years). All patients were Caucasian.

The age of HS ranged from 3 months to 20 years. We classified HS as (1) young HS, HS less than or equal to 1 year of age; (2) fully developed HS, HS aging more than 1 year and less than 3 years of age; and (3) old HS, HS equal to or more than 3 years of age. The age of K ranged from 6 months to 10 years. Skin biopsies were taken from each recruited patient after informed consent, and the study was approved by the ethics committee of the University of Florence. Skin samples were divided into three parts and processed for light microscopy, electron microscopy, and immunohistochemistry.

Light microscopy

The specimens were fixed in buffered-formalin liquid for 12–24 h, routinely processed, and embedded in paraplast plus with a melting temperature of +56°C (Monoject Scientific Inc., Athy Co. Kildare, Ireland). Sections (4- to 6-µm thick) were stained with hematoxylin and eosin and periodic acid–Schiff (PAS)-reaction.

Electron microscopy

The material for the submicroscopic investigation was cut into 1-mm^3 blocks, quickly fixed in 2.5% glutaraldehyde in 0.1 mol/l sodium cacodylate buffer (pH 7.4) for 3 h at +4°C, and post-fixed in 1% OsO_4 in 0.1 mol/l veronal acetate buffer (pH 7.4) for 1 h. The pieces of tissue were stained en bloc through immersion in 2% uranyl acetate in 50% ethanol, dehydrated in increasing concentrations of ethanol, cleared in propylene oxide, and embedded in epoxy resin. Semi-thin sections, 0.5–1 µm in thickness were cut from each block using a Leica Ultracut R ultramicrotome and a diamond knife, and stained with toluidine blue. Ultrathin serial sec-

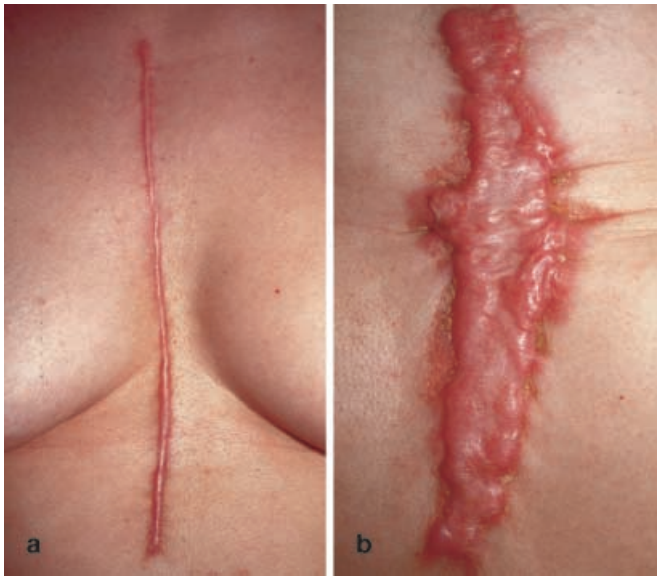


Fig. 1 (*Left*) Hypertrophic scar of the sternal area. The scarring process is limited to the boundaries of the original wound. (*Right*) Keloid of the sternal area. The scarring process invades the skin surrounding the original wound

Table 1 Antibodies used. *N.A.* not applicable

Antibody	Cluster of differentiation	Antibody specificity
T3[a]	CD3	T cells
UCHL-1[a]	CD45RO	T-cell subset
T4[a]	CD4	Helper/inducer T cells
OKT8[a]	CD8	Suppressor cytotoxic T cells
OKT6[a]	CD1a	Langerhans cells, T-zone accessory cells
HLA-DR[a]	N.A.	Class II molecules
OKM5[b]	CD36	Thrombospondin receptor (dermal dendrocytes)
MHM24[a]	CD11a	LFA-1 (α chain)
MHM23[a]	CD18	LFA-1 (β chain)
CL-106[a]	CD54	ICAM-1
1A4[c]	N.A.	α-Smooth-muscle actin
Anti-desmin (Clone 33)[d]	N.A.	Intermediate filaments of muscle cells
Anti-fibronectin[a]	N.A.	Fibronectin
Anti-vimentin (clone V9)[d]	N.A.	Intermediate filaments of mesenchimal cells

[a] Dako, Glostrup, DK
[b] Harlan Sera-Lab Ltd., Belton Loughborough, GB
[c] Sigma Chemical Co., St. Louis, Mo.
[d] BioGenex, S. Ramon, Calif.

tions, cut at 60 nm, mounted on formvar-coated Cu/Rh grids, were stained with uranyl acetate and lead citrate, and examined in a Philips 410 LS transmission electron microscope at 80 kV accelerating voltage.

Immunohistochemistry

The immunohistochemical study was performed either on 4-µm paraffin sections or on 6-µm cryostat sections. Tissue sections were stained using either an immunoperoxidase or the alkaline phosphatase anti-alkaline phosphatase (APAAP) method [6]. The antibodies used are listed in Table 1.

For a quantitative evaluation of the immunohistochemical reactions, the percentage of stained cells in five consecutive microscopic fields were counted by two independent observers using a ×25 objective, and the mean values were calculated and recorded. Only cells in which the nucleus was in the plane of the section were counted.

Results

Light microscopy

The results obtained for light microscopy are shown in Table 2. In both HS and K, the epidermis was slightly flattened with adnexal displacement secondary to the fibrous proliferation. Both lesions showed an abnormal accumulation of connective tissue and an increased density of blood vessels and cells.

We documented some differences in the organization and orientation of the connective tissue and cells between HS and K. The histological profile of HS was found to be related to the age of the examined lesion (Fig. 2). Young HS presented a high number of spindle-shaped cells diffusely permeating the repairing area, without a clear-cut nodular pattern. Fully developed HS were characterized by the frequent presence of distinct collagenous-cellular nodules [9]. Old HS showed widespread collagenization phenomena with the frequent occurrence of collagenous nodular structures (collagenous nodules) with few scattered spindle-shaped cells. Conversely, the histological profile of K was not found to be related to the age of the lesion examined and was characterized by a diffuse cellularity (92% of cases) and the presence (96% of cases) of abnormally thick, hyalinized collagen fibers, haphazardly oriented (Fig. 3). This peculiar type of collagen fibers was never found in HS and was ubiquitously observed within K, although more abundant in central areas of the lesions; in particular, this change was already identifiable in young (6-month-old) lesions. Collagenous-cellular nodules also were found in K (58% of cases), while collagenous nodules were only occasionally found (8% of cases). These last features were generally compartmentalized within the lesions.

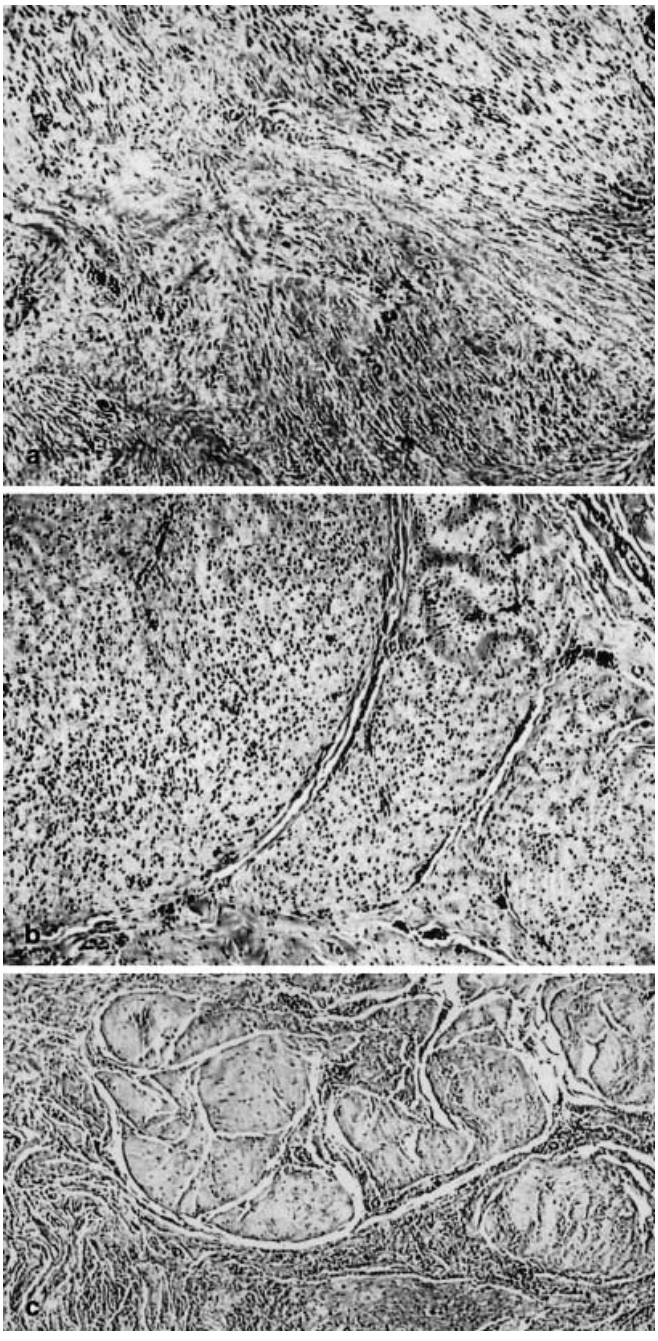


Fig. 2 (*Top*) Young hypertrophic scar. Spindle-shaped cells diffusely permeate the repairing area (hematoxylin and eosin, original magnification ×100). (*Middle*) Fully developed hypertrophic scar. Typical collagenous-cellular nodules (hematoxylin and eosin, original magnification ×100). (*Bottom*) Old hypertrophic scar. Typical collagenous nodules with few scattered spindle-shaped cells (hematoxylin and eosin, original magnification ×50)

Immunohistochemistry on paraffin-embedded sections

The immunohistochemistry results obtained from the paraffin-embedded sections are shown in Table 2. In both HS and K, the spindle-shaped cells, irrespective of their architectural pattern, showed a vimentin$^+$ desmin$^-$ phenotype. In young HS, the large majority (>60%) of spindle-shaped cells – architecturally disposed in a diffuse pattern – showed an α-SMA$^+$ phenotype with a marked immunoreaction for fibronectin (FN) on their

Table 2 Morpho-phenotypic features of pathologic scars. *HS* hypertrophic scar; –=0–5% positive cells; +=6–30% positive cells; ++=31–60% positive cells; +++=>60% positive cells

Type of lesion (number)	Hyalinized collagen fibers	Diffuse cellularity	Collagenous-cellular nodules	Collagenous nodules	α-Smooth muscle actin	Fibronectin
Young HS (10)	0/10	10/10	0/10	0/10	+++ (10/10)	+++ (10/10)
Fully Developed HS (11)	0/11	0/11	11/11	0/11	+ (4/11); ++ (7/11)	+++ (11/11)
Old HS (7)	0/7	0/7	0/7	5/7	– (7/7)	– (7/7)
Keloids (26)	25/26	24/26	15/26	2/26	– (5/26); + (6/26); ++ (5/26); +++ (10/26)	++ (9/26); +++ (17/26)

Table 3 Immunophenotypic features of the immune-cell infiltrate. *HS* hypertrophic scar; –=0–5% positive cells; +=6–25% positive cells; ++=26–40% positive cells; +++=>40% positive cells

Antibody	Young HS (10)	Fully developed HS (11)	Old HS (7)	Keloids (26)
CD3	++	+	– (4/7); + (3/7)	++
CD45RO	++	+	– (6/7); + (1/7)	++
CD4	++	+	– (4/7); + (3/7)	++ (19/26); +++ (7/26)
CD8	– (8/10); + (2/10)	– (9/11); + (2/11)	–	– (20/26); + (6/26)
CD1a	– (7/10); + (3/10)	– (9/11); + (2/11)	–	– (16/26); + (10/26)
HLA-DR	+++	++	+	+++
CD36	++	+	– (5/7); + (2/7)	++
CD11a	++	+	–	++
CD18	++	+	–	++
CD54	++	+	–	++

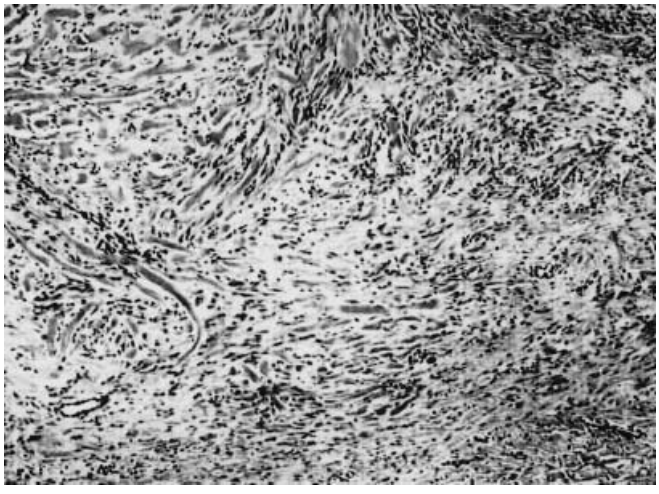


Fig. 3 Keloid. The hallmark of this type of pathologic scar is represented by the presence of a diffuse cellularity and abnormally thick, hyalinized collagen fibers, haphazardly oriented (hematoxylin and eosin, original magnification ×100)

surface. In fully developed HS, α-SMA was expressed in a variable amount of cells (5–60%), while FN was constantly more expressed (>60% of spindle-shaped cells; Fig. 4). In old HS, the few cellular elements contained in collagenous nodules were virtually α-SMA$^-$ and FN$^-$. In K, a variable expression of α-SMA was documented, with no identifiable relationship with the age of the lesion. α-SMA$^+$ cells were present particularly in collagenous-cellular nodules. In five of 26 cases, α-SMA expression was virtually absent. A marked immunoreaction for FN was constantly documented on the surface of a large amount of spindle-shaped cells (Fig. 5).

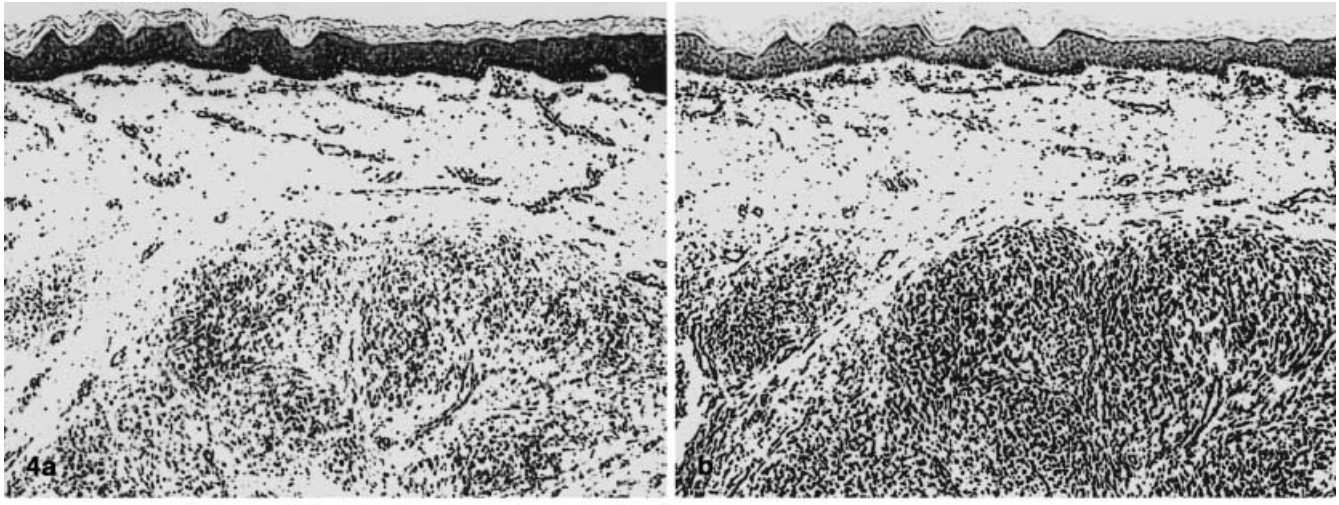
Immunohistochemistry on cryostat sections

The immunohistochemistry results obtained from the paraffin-embedded sections are shown in Table 3. In the dermis of both HS and K, we found an immune-cell infiltrate composed of CD3$^+$, CD45RO$^+$, CD4$^+$ T lymphocytes associated with CD1a$^+$/CD36$^+$ dendritic cells. Functional meaningful molecules were constantly expressed both by T cells [human lymphocyte antigen (HLA)-DR, lymphocyte function associated antigen (LFA)-1/CD11a/CD18] and dendritic cells [HLA-DR, intercellular adhesion molecule (ICAM)-1/CD54]. We found a large amount of cellular infiltrate in young HS; the amount of the cellular infiltrate progressively decreased in fully developed HS and in old HS, where we found a very low quantity of immune cells. Conversely, in K, we found a large amount of the cellular infiltrate both in young and in old lesions; the amount of immune cells was constantly higher than that observed in all types of HS (Fig. 6).

Electron microscopy

In young and fully developed HS, myofibroblasts were found to be the predominant cell type. These cells were characterized by the presence of microfilament bundles peripherally located and oriented parallel to the cell surface. These cells presented typical fibronexa, the peculiar cell-to-matrix junctions of myofibroblasts. Conversely, in old HS, only fibroblasts/fibrocytes showing variable amounts of rough endoplasmic reticulum were seen.

In K, myofibroblasts were found to be the predominant cell type, irrespective of the age of the lesion exam-



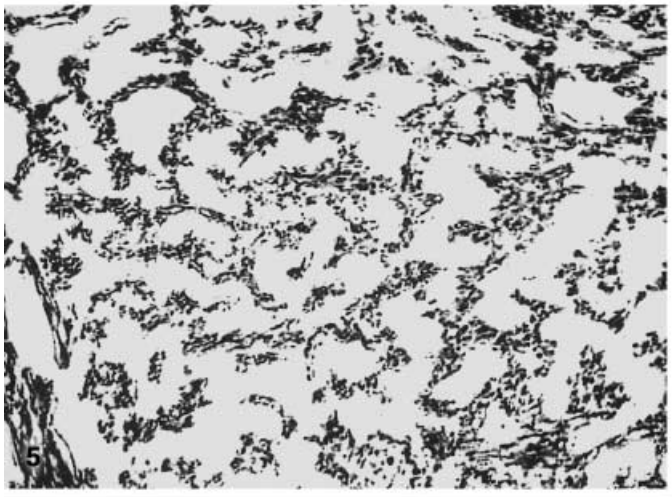
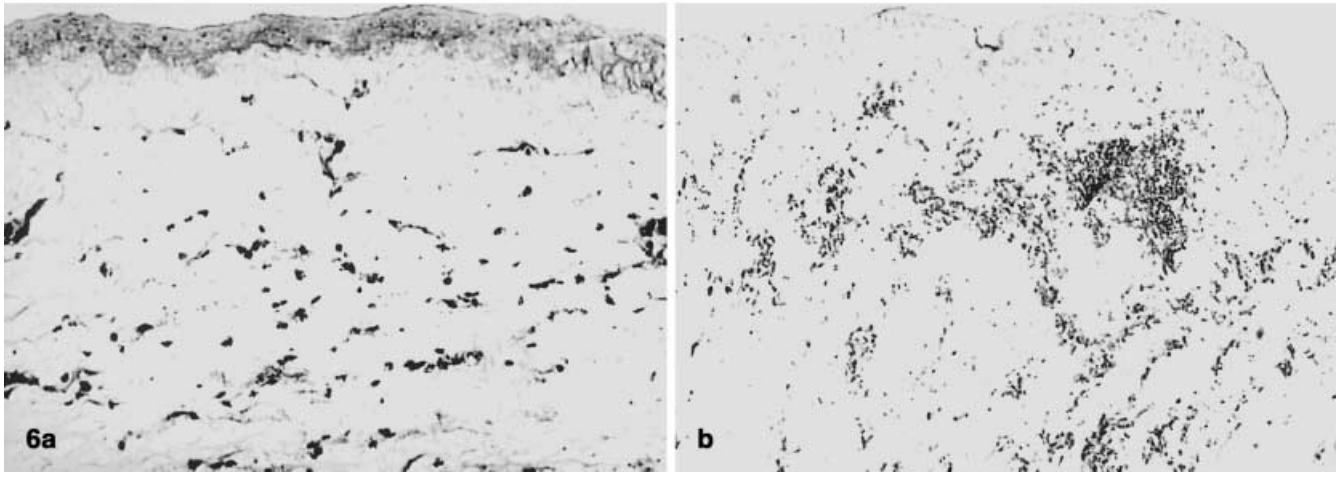


Fig. 4 Fully developed hypertrophic scar. Spindle-shaped cells show an evident immunoreaction for both α-smooth muscle actin (*left*) and fibronectin (*right*). Note the more diffuse positivity for fibronectin [alkaline phosphatase anti-alkaline phosphatase (APAAP) method, original magnification ×100]

Fig. 5 Keloid. Marked immunoreaction for fibronectin, in an α-smooth muscle actin negative keloid [alkaline phosphatase anti-alkaline phosphatase (APAAP) method, original magnification ×100]

Fig. 6 (*Left*) Young hypertrophic scar. A high number of $CD4^+$ T lymphocytes is evident in the dermis [alkaline phosphatase anti-alkaline phosphatase (APAAP) method, original magnification ×100]. (*Right*) Old keloid. Higher numbers of $CD4^+$ T lymphocytes are present relative to young hypertrophic scar (APAAP method, original magnification ×100)



ined (Fig. 7); they were particularly numerous in the collagenous-cellular nodules.

Discussion

HS and K are both aberrations of the wound healing process. The histological distinction between HS and K is still controversial because of the absence of reliable and standardized differential morphologic criteria [12, 26, 29]. Moreover, the terms HS and K have been inconsistently and interchangeably used by clinicians in describing excessive scarring, despite the assumption that they require distinct therapeutic strategies. An insight into the differential diagnosis of pathologic scars was recently obtained by recognizing distinct histological and immunohistochemical differences between HS and typical K of a black population. In particular, HS were found to

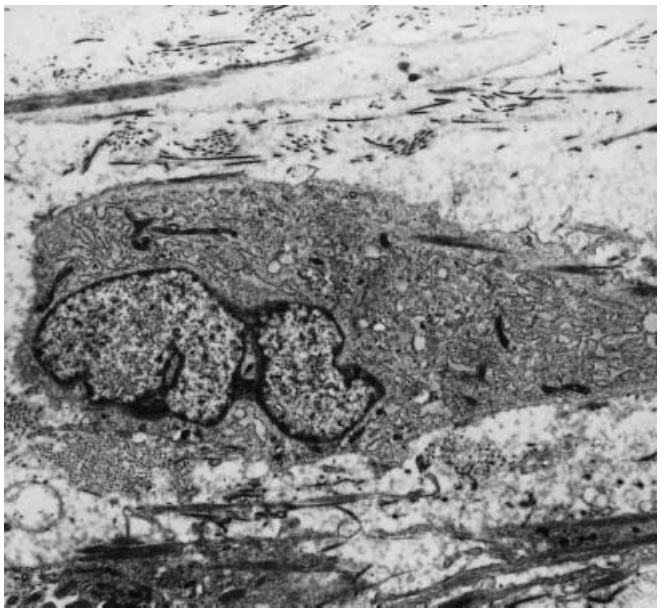


Fig. 7 Myofibroblasts, with the presence of typical, thin, actin-type microfilament bundles peripherally located and oriented parallel to the cell surface and fibronexa in an α-smooth muscle actin negative keloid

contain constantly collagenous-cellular nodules composed of α-SMA$^+$ myofibroblasts. In contrast, K exhibited peculiar, thick, hyalinized collagen fibers, and were composed of α-SMA$^-$, spindle-shaped, fibroblastic cells [9].

The purpose of the present study was to further investigate these differences in Caucasians, taking into account the age of the lesions and possibly to identify additional morpho-phenotypic features, helping to discriminate between these two scars. We have made a rigorous selection of cases, strictly according to the clinical definition of HS and K [7, 23, 27, 29] and taking into account the age of the lesions examined. Our findings define, with more precision than previous work, the time of α-SMA expression in HS and indicate that K of Caucasians exhibit a somehow mixed appearance relative to those of Africans, since they show some features (e.g. cellular-collagenous nodules) previously attributed only to HS [9].

The finding that the histopathological profile of HS is largely related to the age of the lesion examined is in agreement with its clinical evolution, frequently ending in complete regression. Hence, the knowledge of the age of the lesion examined is crucial for the correct evaluation of the morphologic picture of HS.

Conversely, K of Caucasians show different histological features in different areas of the same lesion, and their histological profile is not related to the age of the lesion examined. In agreement with the previous findings of Blackburn and Cosman [4], we confirmed that their histological hallmark is the presence of abnormally thick, hyalinized collagen fibers, haphazardly oriented. In particular, we show that this peculiar type of collagen fibers is already present in young (6-month-old) K and suggest that this is the cardinal criterion for the histological identification of K. Our observations also suggest some caution in the differentiation between HS and K only on the basis of the presence of collagenous-cellular nodules, at least in Caucasians, even though the presence of collagenous-cellular nodules in a lesion aging more than 3 years strongly favors a diagnosis of K instead of HS.

This investigation evidences some peculiar immunohistochemical differences between HS and K. Young and fully developed HS are characterized by the presence of large numbers of α-SMA$^+$, FN$^+$ spindle-shaped cells architecturally disposed in a diffuse or nodular pattern, according to the age of the lesion examined. Conversely, in old HS, the cellular component is inconspicuous, and the few spindle-shaped cells observed are virtually α-SMA$^-$ and FN$^-$. In K, α-SMA$^+$, FN$^+$ spindle-shaped cells are also commonly found, especially in the collagenous-cellular nodules. However, their amount is variable and not related to the age of the lesion investigated. Interestingly, in K, where α-SMA$^+$ cells have not been found (5 of 26, 19%), a marked immunoreaction for FN is constantly documented on the surface of a significant amount of spindle-shaped cells.

The cell surface staining for FN in both HS and K could be considered indicative of the presence of fibronexa, the peculiar cell-to-cell and cell-to-matrix junction typical of myofibroblasts [10]. Therefore, the FN$^+$ spindle-shaped cells, found in both HS and K, can be considered myofibroblasts, irrespective of the expression of α-SMA, possibly in different phases of evolution [30]. This interpretation is supported by our electronmicroscopic findings, which documented the presence of typical myofibroblasts in both young/fully developed HS and K and in the latter group even in α-SMA$^-$ lesions.

Another relevant result of our study is the immunophenotypic characterization of the immune-cell infiltrate constantly found in both HS and K. The cellular infiltrate was composed of CD3$^+$, CD45RO$^+$, CD4$^+$, HLA-DR$^+$, and LFA-1$^+$ T lymphocytes, strictly associated with CD1a$^+$/CD36$^+$, HLA-DR$^+$, and ICAM-1$^+$ dendritic cells. These phenotypic features are indicative of a delayed-type immune reaction and support the hypothesis that immunological mechanisms are involved in the pathogenesis of pathologic scars, and that cell-mediated, major histocompatibility complex (MHC)-class II-restricted immune responses may play an important role in HS and K [5, 13, 15, 18, 25, 26]. Both in vivo and in vitro studies have demonstrated that T lymphocytes and macrophages possess the capacity to regulate essential steps in the process of wound healing and exert a regulatory influence over fibroblast activity [3, 8, 21]. Kischer demonstrated that K transplanted in nude mice undergo a rapid decrease in size, despite retention of the original histological features [16]. Our results demonstrate that the amount of the immune-cell infiltrate is related to the age and clinical behavior of HS. The cellular infiltrate was found in higher amounts in young lesions – which are generally red and enlarging – than in old HS – which

are generally variably regressed and white. In K that remain red, itchy and can also grow after many years, the infiltrate is more conspicuous than in HS of corresponding age and is still present in large amounts in old lesions. Therefore, a relationship could be hypothesized between the amount and function of the immune-cell infiltrate and the activity and differentiation of fibroblasts/myofibroblasts through the production and release of different cytokines that influence the development of pathologic scars.

In conclusion, our study documents that HS are characterized by different histopathological profiles related to the age of lesions, whereas the histological profile of K in Caucasians is not related to the age of lesions and is characterized by the early presence of thick and hyalinized collagen bundles frequently associated with nodules containing myofibroblasts. An immune-cell infiltrate persists in old K. Further investigations are needed in order to examine the presence in these lesions of growth factors and cytokines known to influence the evolution of fibroblastic to myofibroblastic cells [30]. In any event, it appears that when using the proper morphologic and immunophenotypic criteria, HS and K of Caucasians can be reliably differentiated, and the affected patients can be properly selected for specifically tailored therapeutic strategies.

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