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Keloids: Which Types Can Be Excised without Risk of Recurrence? A New Clinical Classification

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Background: A surgical team from Interplast-Germany removed 387 keloids in 302 patients during 4 visits to Goma, Democratic Republic of the Congo, from 2015-2018. Preoperative and postoperative photographs and a thorough anamnesis of keloids were done for all patients. In addition, 18 selected biopsies from 4 types of keloids were histologically examined in Germany.
Methods: Treatment options were tested and keloid recurrence rates were compared with data from questionnaires, photographs, and histology.
Results: Keloids were classified accordingly as follows: (1) fresh nodular (continuously growing) keloids had a 30% recurrence rate after surgery: no common adjuvant therapy but triamcinolone acetonide (TAC) injections on onset, only; (a) earlobe keloids had the lowest recurrence rate after complete excision with negative resection margins; (2) superficial spreading (or butterfly) keloids were treated with TAC injections only; (3) mature (nongrowing or burned-out) keloids had also a low recurrence rate of 4.5%, which were then treated with TAC on onset, only; and (4) multiple keloids comprise various types in different stages.
Conclusions: According to this classification, about 50% of keloids may be removed surgically without risk of recurrence in the examined patient population in Africa, where only TAC injections, but no radiation, are available. Adjuvant TAC or radiation should be started at the onset of recurrence and not generally. *(Plast Reconstr Surg Glob Open 2020;8:e2582; doi: 10.1097/GOX.0000000000002582; Published online 25 March 2020.)*

INTRODUCTION

Genetically, Africans, Asians, and Native Americans have a higher incidence of keloids when compared with whites.[1] Keloids have a higher degree of melanin pigmentation than the surrounding tissue, and melanocytes appear to be crucial in keloid development. Persons with albinism[2] and animals do not develop keloids; however, there is currently a lack of experimental research.

Because keloids do not show spontaneous regression—like hypertrophic scars—an abundance of literature is concerned with therapeutic possibilities (corticosteroid and 5-FU injections, cryotherapy, x-radiation up to 40 Gy, brachiotherapy with 20 Gy, laser, and pulsed dye laser), with physiological data (growth factors, enzymes, inflammatory mediators, genetic markers, and androgens[3]) and histological differentiation (broad collagen fibers, myofibroblasts, apoptosis, and differentiation from hypertrophic scars[4]). However, we are not aware of any publication that differentiates keloids according to history or origin, location, duration (fresh or old), or clinical appearance (hard or soft). Instead, keloids are always described as one pathological entity with one common rate of recurrence between 19% and 45%.[5]

Because preoperative photographs from Goma, Democratic Republic of the Congo, had shown a high number of patients with keloids of various types, a study was designed to reveal which type of keloid may be removed surgically without need of further treatment and which type of keloid is prone to recurrence requiring postoperative triamcinolone Triamcinolon acetonide (TAC) injections.

Clinical Appearance of Keloids

Keloids present clinically as firm, rubbery, fibrous tumors within the site of prior injury or infection of the skin. They appear generally 3–9 months posttrauma, extend far beyond the area of a pustule or shaving injury, and do not spontaneously regress. They generally continue to grow over years and possibly decades.

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Keloids tend to occur in skin sites of higher melanocyte density. During wound healing, intense inflammation activates melanocyte proliferation and melanin production.[6] Genetic factors play a role in populations prone to keloids which may originate from an injury to the dermis alone, such as hypertrophic scarring, or the typical unilateral keloid of the earlobe. Environmental factors include bacterial infection (most often unrecognized) following pustules, small trauma, or burns.

Histology

Keloids are of heterogeneous phenotype influenced by race, age, cause, hormonal state, and duration. Classic histologic findings demonstrate broad, irregular hyalinized collagen bundles with an increased type I/III collagen ratio, decreased fibrillin-1 and decorin expression, increased myxoid extracellular matrix substances, increased dermal cellularity with numerous fibroblasts in pathological density, but few inflammatory cells in the stroma. In the papillary dermis, keloids show a tongue-like advancing edge that resembles invasive benign tumor growth (Fig. 1).

During their growth period, keloids contain inflammatory cells in an inflammatory disorder of the reticular dermis.[7] Certain regulators of the fibrotic cascade, such as transforming growth factor β and fibronectin, have been shown to play a role in collagen deposition during keloid development.[6] An overproduction of multiple fibroblast proteins is an indication of the persistence of wound healing or failure to downregulate wound-healing cells.

The differentiation of keloids from hypertrophic scars is a clinical diagnosis and needs no histological confirmation. A comparison of numbers and magnitude of several organelles of endothelial cells suggest that keloids may be more similar to mature scars.[8] Pathologists make a histological distinction between keloids and hypertrophic scars on the basis of thick eosinophilic (hyalinizing) collagen bundles called "keloidal collagen" and the number of blood vessels.[4] In contrast, the collagen fibers of hypertrophic scars are less broad and run rather parallel to the epidermis, contain many myofibroblasts and fibroblasts, and have low vascularity.[9]

Treatment Possibilities

Surgical Removal

The standard treatment of keloids is surgical excision followed by immediate radiation or additional TAC injections as recurrence becomes obvious (Fig. 2). In Congo, radiation therapy is hard to come by and compliance is low.

Excision of a keloid may stimulate additional collagen synthesis, prompting quick recurrence as a possible larger keloid than the initial one. For this reason, intramarginal surgical (core) excision of keloid tissue has been recommended to prevent stimulation of additional collagen synthesis.[9–12] Tan et al[13] have shown, however, that leaving a small margin of keloid skin in place will rather stimulate a recurrence similar to residues in tumor excision stimulating tumor regrowth. Intramarginal core excisions may only be successful in mature keloids with low recurrence rate; otherwise, it contradicts common tumor surgery.

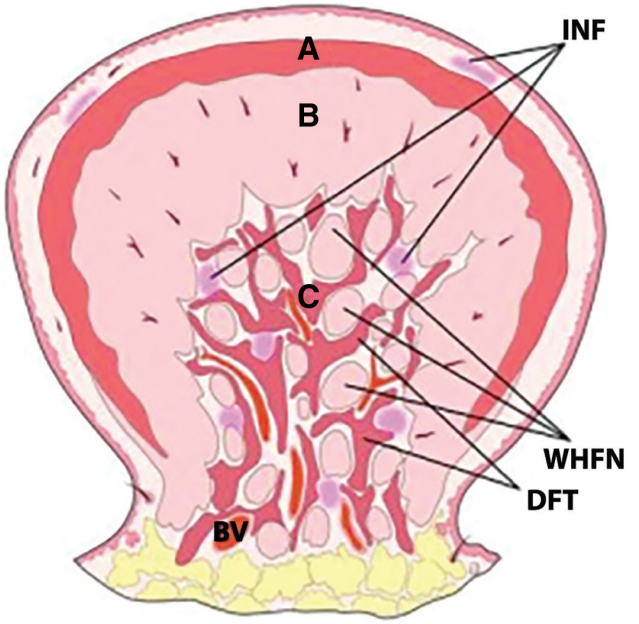

Fig. 1. Microarchitecture of auricular keloids. A, keloidal collagen; (B) organizing collagen; (C) proliferating core collagen. BV, blood vessel; DFT, dense fibrous collagen tissue; INF, inflammatory cell infiltration; WHFN, whirling hypercellular fibrous micro nodule. Part of Fig. 2 in Chong et al.[24]

Triamcinolone and 5-FU Injections

Corticosteroids have suppressive effects on the inflammatory process during wound healing; they reduce collagen and glycosaminoglycan synthesis, inhibit fibroblast growth and TGF-β1 expression, and enhance collagen degradation.[6,14]

In dermatology, current first-line therapy is intralesional corticosteroid injection alone or in combination with other treatment modalities.[14] TAC is the most commonly used intralesional corticosteroid (Fig. 2). The response to corticosteroid injection alone is variable with a 70%–90% regression rate, but with a 33%–50% recurrence rate after 1 and 5 years.[15]

The combination of TAC with 5-FU is more suitable for the treatment and prevention of hypertrophic scars and keloids, showing better improvement in scar height and patient satisfaction as well as having fewer side effects.[16] The occurrence of skin atrophy and telangiectasia in the TAC group was significantly lower in the 5-FU group.[17]

The question whether TAC postoperative therapy is more effective if given early (after 2 wks) or later at keloid reappearance has been answered by Song,[18] who found that the treatment efficacy was significantly improved

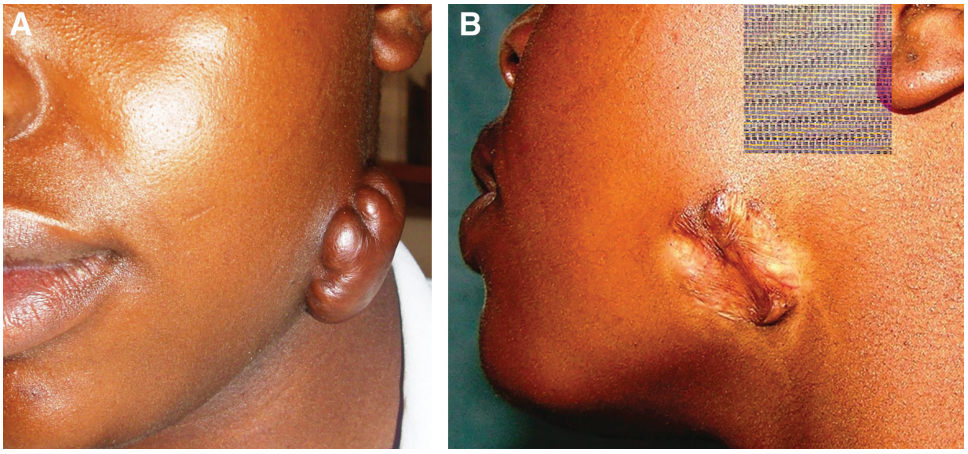

Fig. 2. The effect of monthly triamcinolone injections. A, Fresh keloid, growing for 4 years. B, Six months after 4 sessions of TAC injections.

when applied later during the static stage of pathological scarring.

Radiation and Brachytherapy

Radiotherapy acts primarily by suppressing fibroblast activity and angiogenesis, which prevents the formation of dysfunctional blood vessels and decreases inflammation, thereby suppressing keloid development. Although 54% of keloids recurred after surgical excision alone,[5] postoperative brachytherapy with Iridium-192 yielded the lowest recurrence rate of 15% among the different types of radiotherapy.[19,20] Treatment with a biologically equivalent dose of 20 Gy in 10 or 5 fractions yielded superior local control over lower dose regimens.[21]

However, a systematic literature review of 25 studies of surgical excision of ear keloids revealed a recurrence rate of 15.4% after triamcinolone injections and 14.0% after radiation treatment,[22] that is, showing no significant difference.

MATERIALS AND METHODS

Patients

Patients were recruited from the Eastern Congo region through radio and television and treated in the small CEDIGO Hospital in Goma, Democratic Republic Congo. The majority were patients with huge tumors and severe burn contractures. However, more than 600 patients with keloids were evaluated for this study: 148 patients were rejected due to flat butterfly keloids (Fig. 3), insignificant cosmetic problems, or an excess number of keloids. Three hundred two (246 females and 56 males) patients were screened for surgical removal and eventual postoperative TAC injections. Preoperatively, the 302 keloid patients were divided into 183 risk free and 119 risky, that is, candidates for eventual postoperative TAC injections (Table 1).

The principles outlined in the Declaration of Helsinki have been followed. The Health Ministry of the State of Kivu North has been informed of this study. No ethics Committee has been established in Goma.

Documentation

Local physicians of the Nazarene Ambulance took meticulous case histories of all patients, noting the duration and cessation of keloid growth, gross type and etiology, bilaterality, family history, treatment (prior surgery and postsurgery), and prior complications. They then analyzed and compared the data with the patients' photographs (by K.E.K and J.S.).

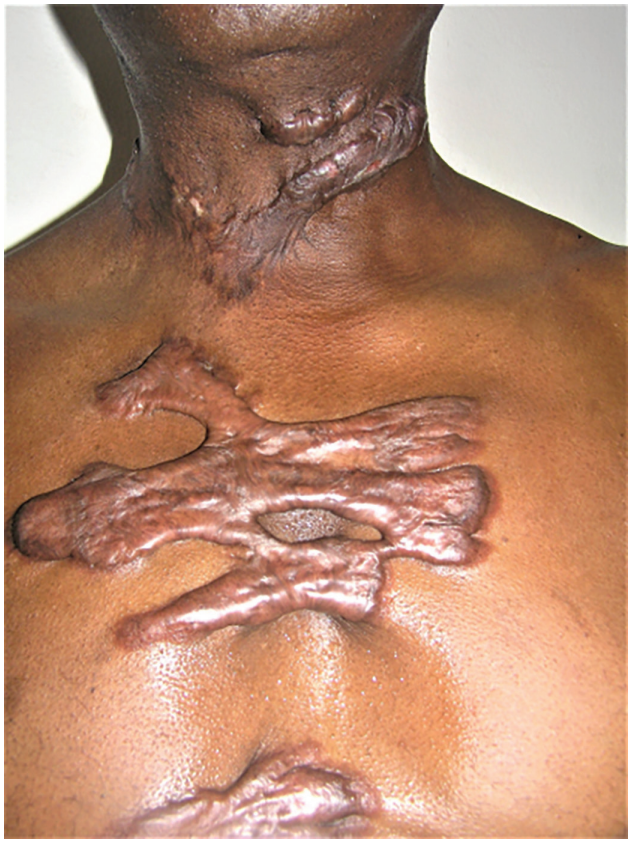

Fig. 3. Extended "butterfly" keloid still growing perpendicular to the main folding lines.[23] TAC has been refused since no pain.

Table 1. Preoperative Keloid Locations in Goma, Congo

Location	Single Keloid	Multiple Keloids	Remembered Infection or Trauma
Earlobe	60	153	141/213 = 66%
Face	23	37	31/60 = 52%
Body	13	124	44/137 = 32%
Extremities	8	34	29/42 = 69%
Total	104 = 23%	348 = 77%	245/452 = 54%

(n = 452 questionnaires).

For reasons of objectivity, all 452 patients determined themselves, which keloids bothered most and should be injected with TAC or surgically removed. One hundred fifty patients were selected for TAC injections only. Three hundred two patients had surgical removal of their keloids in summer 2015–2018. In both groups, maximal 3 keloids per patient were surgically removed or treated with TAC and, however, counted statistically as 1 keloid per patient. Forty-two of 452 (9%) satisfied patients returned for a second or third treatment of more keloids in the following years. Statistically, all 42 were treated as former patients and not counted twice.

Triamcinolone Injections

In most African countries, postoperative radiation is not available or unaffordable for a majority. TAC injections were only applied to nonoperable and flat keloids and at the onset of postoperative keloids but not in hypertrophic scars. Four hundred vials TRIAM-40-Lichtenstein (40 mg/ml vials from Winthrop, Frankfurt am Main, Germany) were diluted with lidocaine and injected as TRIAM-20 with a Dermojet-pistol percutaneously, or through a 27G needle intralesionally in a 3D-fanlike manner in 4-week intervals (Fig. 2).

Surgical Removal

All adult patients underwent surgery under local anesthesia; 4 children received general anesthesia (propofol).

Complete extramarginal excision was to leave up to 5-mm margins of healthy skin—but never a 5-mm margin of keloid skin, as proposed and still adhered to by surgeons and dermatologists worldwide.[10,11] The optimal direction of incisions and wound edges, parallel to the main folding lines of the skin, appeared to be crucial for optimal scarring in patients prone to hypertrophic scarring and recurrences[23] (Fig. 4).

After undermining the surrounding skin for easy closure, the wound edges were closed under tension with absorbable subdermal and nonabsorbable subcuticular sutures; Z-plasties or local flaps were not planned or necessary.

Postoperatively, patients had to return to the ambulance for removal of stitches or subcuticular sutures, and again 1–3 months after surgery for taking photograph, or for triamcinolone injections, when recurrence became apparent.

The compliance rate of 83% was unexpectedly high and it was assumed that the remaining patients (17%) had no keloid recurrences. The study was closed on May 31, 2019, 48 months after the first and 10 months after the last treatment in June 2018. The local surgeons continued to provide all documents on further treatment, complications, recurrences, and subsequent photographs.

Statistical Analysis

The χ^2-test was used for statistical analysis. A P value of less than 0.05 was considered statistically significant.

Table 2. Patients Treated in Goma, Congo (n = 452)

Treatment	Patients Total	Lost Patients after First Treatment	Hypertrophic Scars	Recurrence between 48 and 9 mo
Total treated	452	77/452 = 17%	56/274 = 20%	50/375 = 13%
Patients on TAC	150	26/150 = 17%	None	11/124 = 9%
Total operated	302 (with 387 keloids)	51/302 = 17%	56/251 = 19%	39/251 = 15%
Patients on risk	119	22/119 = 18%	27/97 = 27%	32/107 = 30%*
Patients w/o risk	183	29/183 = 16%	20/154 = 13%	7/154 = 4.5%*

*Highly significant difference ($P < 0.01$).

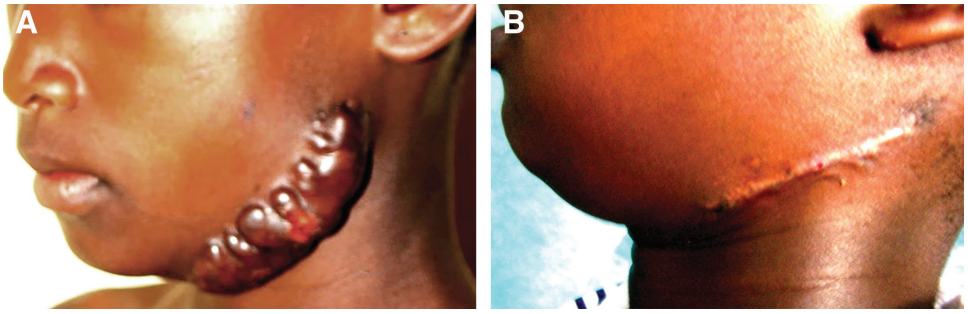

Fig. 4. Excision of a fresh keloid. A, Fresh keloid, still growing and no indication for operation (daughter of nurse). B, Three months after excision in main folding lines, no recurrence.

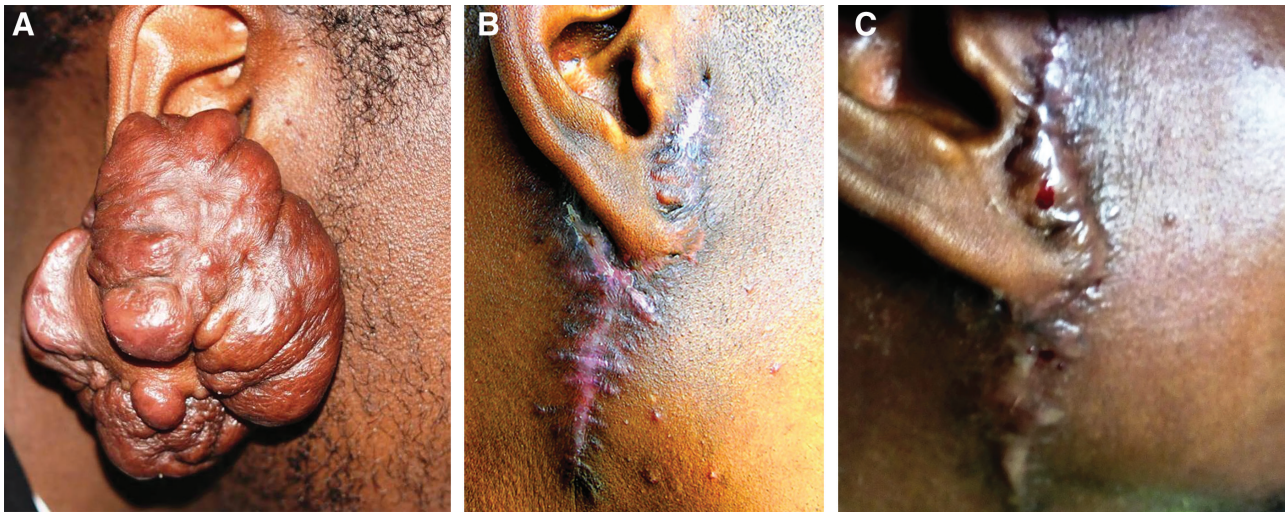

Fig. 5. Excision of a still growing keloid. A, Firm and partly compressible keloid but still growing. B, Hypertrophic scar, 2 months after excision of keloid. C, Keloid recurrence at 4 months, immediate TAC injections.

RESULTS

Questionnaires

An extensive preoperative questionnaire revealed that "spontaneous" keloids were rather unlikely. Fifty-four percent of patients with "butterfly" keloids in their sweat groove over the sternum, shoulders and back remembered having had prior acne, insect bites, or at least itching and scratching on the same sites, supporting the hypothesis of an infectious origin. The majority of patients with nodular ear keloids remembered pain or secondary healing after earlobe sticking (Table 2). The remaining 46% of patients could not remember any prior symptoms.

Length of Existence of Keloids

The onset of keloids in question could rarely be exactly determined and an average time of existence of 7.2 years was estimated for this population. The majority of patients were in their 20s, and some in their 40s and 50s; however, none reported to have had a scar in childhood, which developed into a keloid during puberty. Six women reported that presternal butterfly scars suddenly enlarged during pregnancy and continued growing.

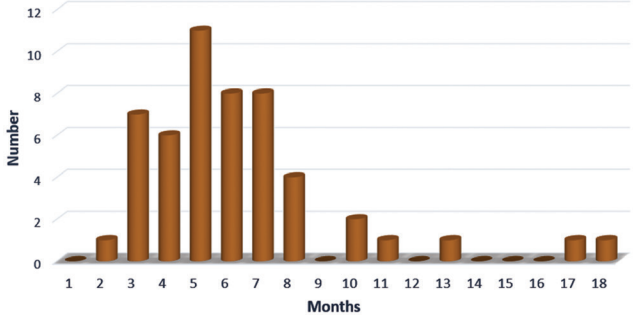

Fig 6. Onset of keloid recurrences in months after surgical removal or last TAC injection (n = 50/375 = 13%).

Results of Surgery

Of 452 treated keloid patients, 302 patients with 387 keloids underwent surgery. Of these, 51 (17%) were lost to follow-up and 274 patients were statistically evaluated. Of 107 selected patients with mainly "fresh" and indifferent keloids, 32 patients (30%) developed suspicious recurrences and were injected with TAC after clear onset during their postoperative phase (Fig. 5).

Among the 154 patients who underwent surgery for "mature" and "burned-out" keloids, only 7 (4.5%) developed incipient keloids after 3–11 months (Fig. 6) and required TAC injections. The difference of 30% recurrences in the "fresh" group and 4.5% in the "mature" group is highly significant ($P < 0.01$) (Table 2).

These low recurrence rates are likely due to a high percentage of patients in Africa who lived with keloids for 10 and 20 years (Fig. 9) compared with patients in developed countries, whose keloids are removed within months of onset.

Fresh Nodular Keloids Treated with TAC Injections

Postoperative TAC injections were only applied when recurrence was clinically obvious and clearly bothersome (pain and itching) because best effects are seen when injected at the onset of hypertrophy rather than in the early postoperative stage.[18]

Earlobe Nodular Keloids

After excision of earlobe keloids, only one recurrence was observed to date (Fig. 5), but some hypertrophic scars in front or behind the ear occurred (Fig. 7). Mothers reported that the common practice of ear lobe piercing in childhood rarely resulted in keloids before puberty. This supports our experience that keloids which develop after bacterial infection of surgical wounds need a kind of hormonal imbalance during puberty and adulthood.[3]

Mature or "No-growth" Keloids

Nodular keloids with a long history of "no-growth" (at least 2 y) and with a soft and loose consistence, described

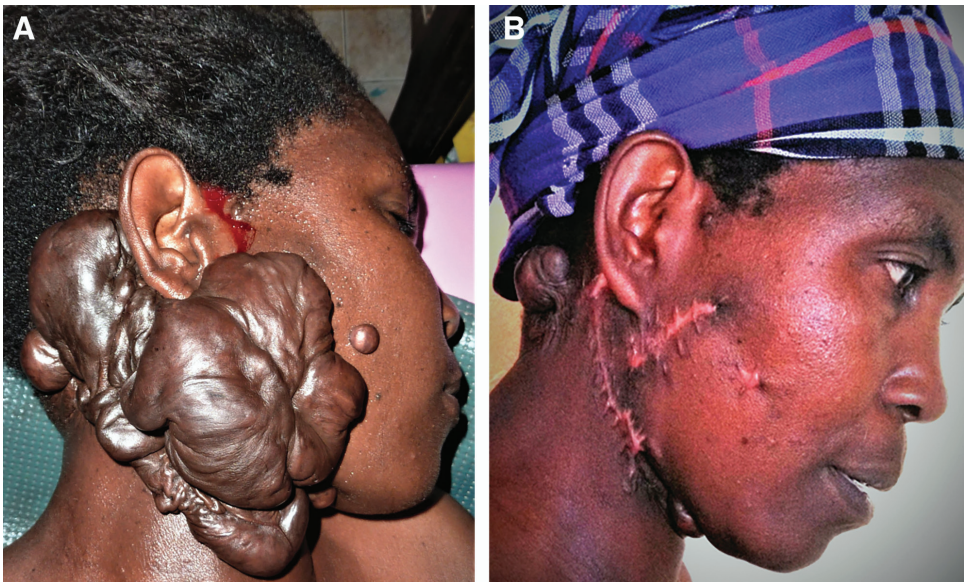

Fig. 7. Excision of a mature keloid. A, Mature keloid of compressible consistency, onset 7 years ago on one earlobe only. Stopped growing 2 years ago. B, Receding hypertrophic scars 12 months after excision.

as "mature" or "burned-out", showed by far the lowest rate of recurrence (7/154 = 4.5%) (Fig. 7).

These facts lead to the recommendation to pay more attention to a patient's anamnesis (when did the keloid stop growing?) and consistence of the keloid (hard or soft and centrally depressed?) when considering surgical removal. Firm, hard, and growing keloids have a high risk of recurrence (32/107 = 30% in our preselected series) (Fig. 8), whereas soft, depressed, and old appearing keloids do not recur (Fig. 9).

Histology of 16 Biopsies

The gross histological picture of keloids resembles fibromas. In fresh keloids, overactive fibroblasts produce high amounts of collagen and growth factors. The collagen fibers are disorganized, large but rather slim, and hyalinized (types I and III) collagen bundles with no nodules and few myofibroblasts. Vascularization is poor with widely scattered dilated blood vessels (Fig. 10A).

In contrast, mature keloids show tightly packed collagen, in parallel broad bundles or in nodules, with less cellularity but higher vascularity (Fig. 10B). Overlapping histological features hampered clear-cut distinction of keloid types.

In general, this histopathological study shows the difficulty to draw conclusions from pathological features to its clinical appearance (Table 3). A more detailed analysis including additional physiological factors is necessary to describe a keloid exactly.

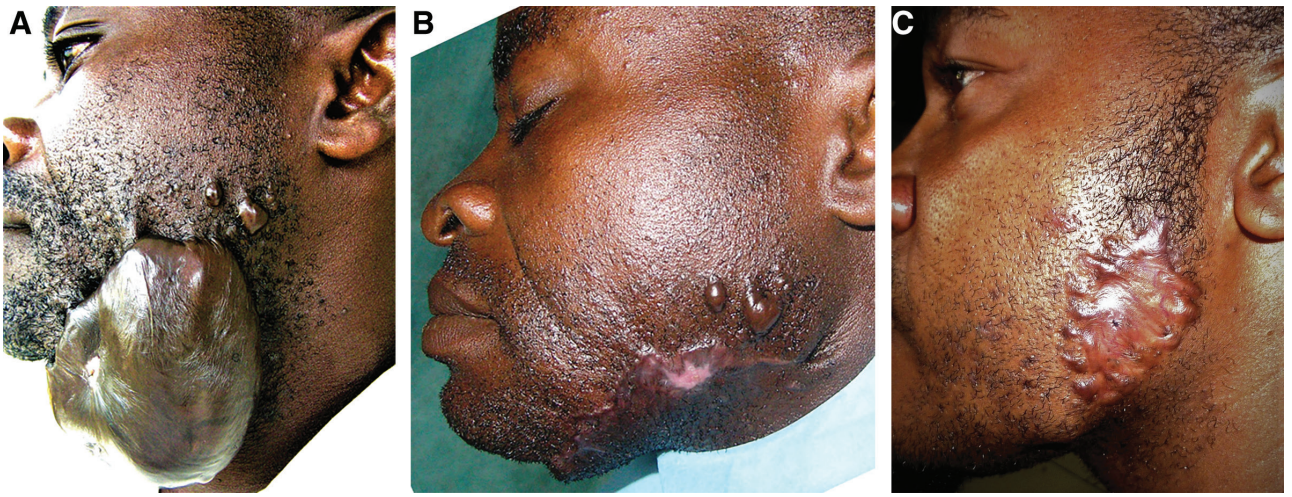

Fig. 8. Case of a still growing keloid. A, Mature keloid, probably resulting from a shaving injury 4 years previously. B, Hypertrophic scar 6 weeks after surgical removal. C, Widened scar 1 year after 2 × TAC injections.

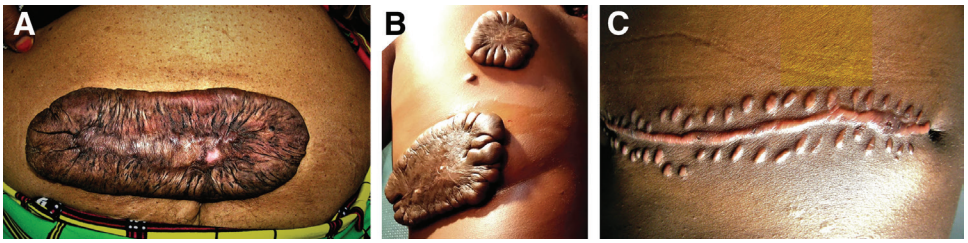

Fig. 9. Different regressing keloids and a hypertrophic scar. A, Old burned-out keloid above umbilicus existing for more than 20 years. Ideal for excission without recurrence. B, Two burned-out keloids on right back with central involution, no growth for 5 years. C, Typical hypertrophic "railroad track" in main folding lines at 6 months. No signs of keloid recurrence.

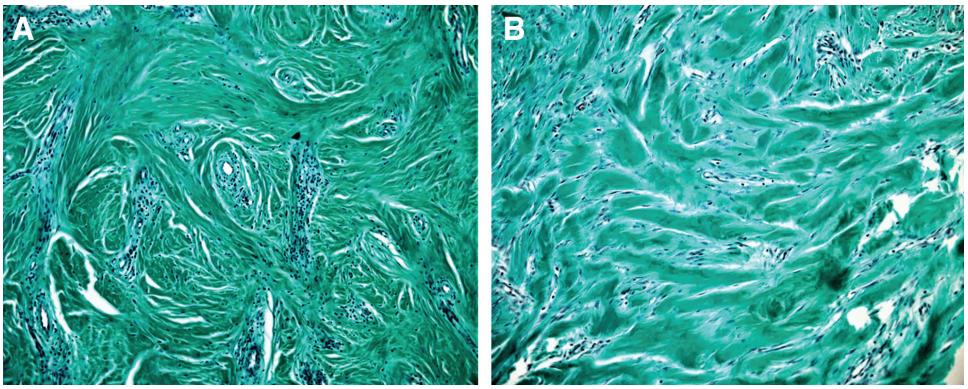

Fig. 10. Histology of keloids. A, Fresh keloid from nape of neck. Collagen bundles in whirls, poor hyalinization, marked perivascular inflammation (Masson-Goldner staining 200×). B, Mature keloid from earlobe. Broad packed hyalinized collagen bundles and poor inflammatory and proliferative cells (Masson-Goldner staining 200×).

Complications

In one patient, a fresh wound along the mandible opened around day 6 and subsequently healed without hypertrophic scars with the use of topical antibiotic cream. In another patient having undergone nonradical excision, the wound behind the ear opened, appeared to be infected, and was closed surgically after 9 days of topical antibiotic treatment. In this case, TAC injections were started effectively after 4 weeks. Recurrences are common and now predictable and, therefore, are not considered complications but listed in Table 2.

DISCUSSION

The single most important finding of this study is the delineation of the relationship between the surgical resection margin and recurrence. The remnants of keloids from prior surgery may regrow over time, which justifies the practice of routine histopathologic reporting of keloid excision margins.[13]

The importance in preventing keloid recurrence is a careful radical surgical removal, not leaving positive resection margins.[13] In Tan's series of resected ear keloids without recurrence, only 16 of 87 (18.4%) patients had free resection margins, but a large number of patients (76.8%) with positive resection margins also had no recurrence. Probably, most of them were mature keloids. In another series, no tumor recurrence was found in cases with free margins, whereas all 18 (20.7 %) recurred cases had positive resection margins.[24,25]

A second important reason for the prevention is the fact that more than half of our patients remembered a bacterial infection as the cause of their keloid. Especially in Africa, local antibiotics or antiseptics should be applied into the open wound at the end of all operations and earlobe sticking.

Table 3. Histopathological Findings of 16 Biopsies

Type of Keloid	Vessel Density	Stroma Cell Density	Collagen Bundles	Inflammatory Reactions
1. Fresh nodular	Rare	Strong	Fine	Strong and perivascular
2. Flat "butterfly"	Increased	Scattered	Broad	Rare and central
3. Mature and "burned-out"	Increased	Scattered	Broad	Mainly marginal
4. Earlobe keloid	Increased	Strong	Broad	Central and marginal

Table 4. Clinical Types of Keloids

Type of Keloid	Clinical Appearance	Anamnesis	Histology	Treatment
1. Fresh nodular keloid	Firm, growing, no confined borders, itching	Constant growth since months and years	Inflammatory cells, poor vascularity, fine collagen bundles, extracellular matrix	Excision with TAC or radiation—only, if recurrence!
a. Nodular earlobe keloid	Firm, fresh, or mature	Clear bacterial infection; often unilateral	Strong vascularity and broad collagen bundles	Excision, little risk of recurrence
2. Superficial spreading/ "butterfly" keloid	Flat with central regression, telangiectasia	Endless growth at its edges over decades	Myxoid basis, strong vascularity, finger-like infiltration of dermis	TAC injections, only
3. Mature nodular and "burned-out" keloid	Soft, confined boarders, central regression, brain-like edges	"No-growth" Limited borders, regression since years	Packed hyalinized broad collagen bundles, few fibroblasts, few vessels, nodules of homogenized fibrils	Excision with TAC in back hand; "burned-out" have no risk of recurrence
4. Transition keloids	Multiple diverse keloids in different stages	Different onsets and types	All variations possible	Single excisions with TAC in back hand

CLASSIFICATION

Keloids have a variable clinical behavior in response to therapy, and there is no clinical–pathological classification that predicts such varied behavior. A new classification is presented which focuses on the clinical differentiation between keloids (Table 4).

1. Fresh nodular keloids (still growing) shall only be excised with postoperative radiation or TAC injections in the backhand at the onset of recurrence.
   a. Earlobe keloids (always infected) have the lowest recurrence rate when completely excised avoiding any positive margin. Most patients remembered a distinct local infection after sticking.
2. Superficial spreading keloids (butterfly keloids) should be treated with TAC injections in growing margins, only.
3. Mature keloids (nongrowing and burned-out) can be removed surgically, with TAC injections in the backhand when recurrence is clear.
4. Transition keloids cannot be classified immediately, if there are various types, which are fitting in different classes.

Only one novel classification has been suggested so far on earlobe keloids.[26] The classification of earlobe keloids into 5 morphologic patterns describes its frequency of earlobe keloids in descending order as a sessile type, single nodular pattern; pedunculate type; sessile type, multinodular pattern; buried type; and mixed type—and its different surgical excisions. There appears to be no need to propose different surgical techniques for keloids on other locations.

CONCLUSIONS

In conclusion, this prospective study clearly demonstrates the following:

1. A clinical differentiation is possible between mature "burned-out" keloids to be surgically removed without further treatment—and still growing fresh keloids requiring postoperative radiation or TAC injections.
2. Bacterial infection of a surgical wound, burn, acne, pustule, or scratch appears to be the main origin of keloids in genetically prone Africans.
3. Earlobe keloids in African populations show no or a low rate of recurrence after complete excision.
4. Superficial spreading, or "butterfly" keloids can be reduced in height but not in size with TAC injections in 4 weeks sequence.
5. Core excisions, leaving positive keloid margins after excision, make no sense in still growing keloids since a remnant proliferating core will stimulate regrowth—similar to benign tumors; a clear negative extramarginal excision may prevent local recurrence.
6. After surgery, triamcinolone (TAC), crystal prednisolone or betamethasone should be available in case of recurrence within 3–15 months after removal.
7. Radiation treatments could be dispensed with if all patients were selected for surgery according to the above criteria. "Adjuvant" radiation may treat half of the patients in vain, that is, can still be started at onset of recurrence.
8. Histological differentiation of the various keloids did not turn out as significant as expected. Further parameters may demonstrate the difference between fresh and mature keloids.

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