Annals of Plastic and Reconstructive Surgery

Research Article
Published: 02 Sep, 2022

Spontaneous Keloids: A Rare Entity

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Abstract

Purpose: Keloid scars are a benign fibroproliferative disorder resulting from tissue scar inflammation and abnormal collagen accumulation. Spontaneous keloids occur in the absence of an original traumatic condition, with reported cases associated with several genetic syndromes and a positive family history. This review aims to gather these existing cases, organizing them according to their possible etiology and used treatments.

Methods: This review was conducted using PubMed and Web of Science, by using the query ("spontaneous keloids" OR "idiopathic keloids"). No type of filter was applied in the search due to the scarcity of published cases and rarity of this scarring disorder. All case reports and studies related to spontaneous keloids were included and all cases associated with trauma were excluded. In addition, two case reports of this type of keloids were also included.

Results: It was possible to verify an association between spontaneous keloids and some genetic disorders. However, there were cases where individuals are completely healthy. Regarding the types of treatment used, it was shown that most keloids remain highly refractory to therapy with high rates of recurrence.

Conclusion: Idiopathic keloids are an extremely rare condition whose exact etiology is often difficult to determine, although in certain cases it is possible to verify a probable genetic influence on the origin of this type of scar. Despite its refractoriness, nowadays the combination of surgery and postoperative radiotherapy has shown excellent results.

Keywords: Spontaneous keloids; Fibroproliferative disorder; Genetic susceptibility; Trauma; Benign

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Received Date: *08 Aug 2022*
Accepted Date: *26 Aug 2022*
Published Date: *02 Sep 2022*

Citation:
Cabral B, Horta R. Spontaneous Keloids: A Rare Entity. Ann Plast Reconstr Surg. 2022; 6(3): 1097.

Introduction

Keloid is a fibroproliferative skin disorder resulting from an abnormal healing process that generates chronic wound inflammation and a continuous deposition of collagen fibers [1]. The distinguishing feature of keloids from hypertrophic scars is their tendency to invade the surrounding skin, extending beyond the limits of the original wound [2]. They may appear several years after the initial trauma, grow slowly, and almost never regress [3].

The most common areas of the body for the appearance of keloids are those that have a strong or repetitive stretching of the skin, such as the anterior chest, shoulder and ears, being a rare occurrence in the scalp and anterior tibia [4].

Keloids can occur in people of any ethnicity; however they are more commonly seen in Hispanic, Asian [5] and African descent individuals, with an incidence between 6% to 16% in the latter [6]. One study showed a correlation between sun exposure and the development of these scars, with the higher the Fitzpatrick phototype, the greater the propensity for the development of keloids [5].

Although much of the literature argues that keloids affect men and women equally and that there are no significant differences regarding the average age of onset, women have twice the prevalence at almost all ages, including before the age of 15 years old [1].

Keloids are usually the result of trauma but can also be associated with genetic conditions or a positive family history. Much more rarely, they can also arise spontaneously, when there is no history of trauma or surgery [7].

Regarding the histopathological characteristics, keloid scars have a specific presentation, demonstrating an excessive accumulation of hardened collagen fibers (mostly type I) arranged in

clusters [8] and hyalinized.

Asymptomatic or associated with itching, pain and deformation, keloids can lead to a disabling situation both physically and psychologically, with a great impact on the patients' quality of life [6]. It should be noted that although keloids are not considered malignant conditions, some articles argue that they have some cancer-like characteristics that may underlie clinically more aggressive and disfiguring keloids [9].

This fibroproliferative disorder may have its origins in several systemic and local factors, and its pathophysiology is complex and still poorly understood. According to existing knowledge, scar growth appears to be driven by inflammation in the reticular dermis, with consequent accumulation of inflammatory cells and fibroblasts in the scar area. This leads to increased levels of pro-inflammatory cytokines such as Il-6 and TNF-α, promoting a chronic inflammation that is a precursor to the increase in keloid size [3]. Systemic factors such as adolescence and pregnancy, due to hormonal changes and the vasodilator effect of estrogen, will exacerbate local inflammation. Local risk factors such as prolonged healing, wound depth and skin tension can also contribute to this abnormal healing process [4].

In the literature, there are several available treatments for keloids, including medical compressive ointments, intralesional injections of corticosteroids, non-steroidal products, surgical excision, laser treatment, intralesional cryotherapy and postoperative radiotherapy. A combination therapy with surgical excision followed by radiotherapy has emerged as a new method of choice, with a lower recurrence rate (between 6% to 27%) [2]. It is also important to highlight the development of new therapies in the field of genetics, epigenetics and stem cell therapy, which have shown promising results. However, despite this variety of therapeutic options, keloids remain highly refractory lesions, requiring a search for more effective therapies [8].

The purpose of this review article is to collect and compile the reported cases of spontaneous keloids existing in the literature, organizing them according to the existence of genetic susceptibility or other associated medical conditions. In addition, an analysis of the effectiveness of the therapies used in this case reports will be performed, as well as a brief review of treatment options of keloids. Therefore, it is intended to produce a clear review on reported spontaneous keloids, an extremely rare condition universally, with few published cases and many uncertainties to be clarified.

Methods

This review was conducted through a search using the online search engines PUBMED/MEDLINE and Web of Science. The query ("spontaneous keloids" OR "idiopathic keloids") was used and, due to the rarity of this scarring disorder, the scarcity of existing cases in the literature and in order to assure a compilation of the largest number of case reports related to spontaneous keloids, no filter of any kind was applied in the search.

From this stage, all articles resulting from the search and freely accessible were analyzed and chosen after reading the title, abstract or full text.

Thus, all published and accessible case reports and studies performed on humans related to spontaneous keloids were included in this paper, excluding all cases associated with trauma.

In addition, two case reports of two women, one 54 years old and the other 82 years old were included in this review. The first case report is about idiopathic keloid scars located in the posterior region of the left auricle submitted to surgical excision followed by radiotherapy. The second case report portrays multiple thoracic keloids, which have not undergone any medical or surgical treatment.

Thus, we tried to encompass a set of articles that would allow the fulfillment of a paper as comprehensive as possible, enabling a global analysis of the spontaneous keloids possible etiologies and therapies used.

Results

Through the carried out search, it was possible to verify that the concrete etiology of spontaneous keloids is not yet fully known. However, it was possible to verify some conditions that may be present at its origin.

Possible etiologies of spontaneous keloids

With this work, an association between spontaneous keloids and some genetic syndromes became evident, which is confirmed by the current literature (Table 1).

On the one hand, Guleç et al. [10] reported a case of a six-year-old boy with Noonan syndrome who was more prone to develop recurrent keloids on his right foot, which is uncommon in this type of patient. On the other hand, the Goeminne Syndrome represents a new syndrome associated with X, characterized by the presence of congenital muscular torticollis, cryptorchidism, pyelonephritis and extensive spontaneous keloids, as described in the article [11]. Another genetic disorder appears depicted by Haugen and Bertelsen [12], which reported the case of a Norwegian family in which the mother and her two children have conjunctival-corneal dystrophy. In this family, there was a spontaneous emergence of keloid lesions on the hands and fingers in the children and associated with a history of minimal trauma in the mother's case. Also published was the case of a 36-year-old male with a new Filamin A mutation X-associated Syndrome, characterized by valvular heart disease, decreased mobility and spontaneous keloid scarring, in this case on the thighs, hips and back [13]. Additionally, a genetic disease that seems to favor the existence of a hereditary pattern in relation to keloids is X-associated recessive poly fibromatosis. One of the cases described a 40-year-old man with a keloids personal and family history, who suddenly developed multiple keloids on the trunk and extremities at age of 20 [15]. There were also cases of Bethlem Myopathy in a 32-year-old woman and a 50-year-old man, both of whom developed spontaneous keloids on the shoulder [16]. A possible association also arises with Dupuytren's disease, in which the case of a 60-year-old man with a personal history of keloids is reported, who subsequently develops five more keloids, the latter without any history of trauma [17]. Another genetic condition with greater published scientific evidence is the Rubinstein-Taybi Syndrome, widely associated with idiopathic keloids [18-20]. It is also important to mention the case of a seven-year-old boy with Dubowitz Syndrome who suddenly manifested multiple spontaneous keloids at the age of four, without any previous trauma [21]. Also of note is the case of a 27-year-old patient with syndromic facies and mental illness who developed keloids idiopathically at various sites on her body [22].

Despite this relationship with genetically susceptible individuals, there are also cases of this type of keloid reported in individuals

Table 1: Spontaneous keloids associated with genetic disorder.

Condition	Age, years	Race	Gender	Site	Pathophysiology	Treatment	Ref. No.
Noonan syndrome	6	Caucasian	M	Third toe of the right foot	After crushed by a large stone	Surgical excision	[10]
Goeminne syndrome	33	Caucasian	M	Arms, chest and neck	Spontaneous	-	[11]
Conjunctivo-corneal dystrophy	57	Norwegian	F	Hands and fingers	Minimal trauma	Local radiation therapy	[12]
	22		M	Right third finger and left index finger	Spontaneous		
	15		M	Three ulnar fingers			
Novel X-linked syndrome with filamin A (FLNA) mutation	36	Caucasian and Native American	M	Thighs, hips and back	Spontaneous	Topical and intralesional corticosteroids	[13]
Polyfibromatosis with erosive arthropathy	23	Caucasian	M	Chest, back, hands and foots	Spontaneous	Intralesional steroids and radiation therapy	[14]
X-linked recessive polyfibromatosis	40	Australian	M	Trunk and extremities	Spontaneous	Multiple corticosteroid injections	[15]
Bethlem myopathy	32	Caucasian	F	Shoulder region	Spontaneous	-	[16]
	50		M				
Dupuytren's disease	60	Caucasian	M	Toracic wall and anterior abdominal wall	Spontaneous	Intralesional triamcinolone and cryotherapy	[17]
Rubinstein-Taybi syndrome	45	Indian	F	Shoulders, arms, thighs, legs and back	Spontaneous	-	[18]
	18 and his elder brother	Indian	M	Chest, abdomen, shoulders, back and thighs	Spontaneous	-	[19]
	15	Caucasian	M	Presternal area and upper arms and back	Spontaneous	Topical corticosteroids and oral antihistamines Laser beam therapy	[20]
Dubowitz syndrome	7	Caucasian	M	Right neck, right temporal and right infraclavicular areas	Spontaneous	-	[21]

Table 2: Spontaneous keloids without any medical conditions.

Condition	Age, years	Race	Gender	Site	Pathophysiology	Treatment	Ref. No.
Healthy	"Middle-age"	Caucasian	F	Back, Chest, Breasts	Spontaneous	Topical and intralesional corticosteroids and intralesional bleomycin	[27]
Fitzpatrick skin type III						UVA-1 phototherapy in a low-dosage regimen	
Symmetrical keloids on the bilateral labia majora	59	Chinese	F	Bilateral labia majora	Spontaneous	Antibiotic treatment Surgical resection combined with postoperative radiotherapy	[28]
Postauricular keloid	81	Caucasian	M	Postauricular region	Spontaneous	Surgical excision	[29]
Bilateral idiopathic corneal keloid	2	Japanese	M	Bilateral corneal	Spontaneous	Betamethasone and tranilast eye drops Lamellar keratoplasty Corneal and conjunctival peritectomy	[30]
Spontaneous resolution	39	Caucasian	M	Thoracic	Spontaneous	Intralesional triamcinolone	[37]
About a rare case	21	Caucasian	F	Back and chest	Spontaneous	Silicone gel	[31]
Multiple keloids	41	Caucasian	F	Back and lumbar region	Spontaneous	Cryotherapy Surgical excision with intradermal injection of triamcinolone and subsequent radiotherapy	[32]
Unusual histologic features	56	Indian	M	Above the nipple	Spontaneous	-	[33]
	79	Black	F				

with allergic disease. A 34-year-old woman with a history of severe asthma and chronic idiopathic angioedema developed two keloids on her back, without any history of trauma, surgery, or acne [23]. Another case report describes a 24-year-old woman with a history of childhood asthma, pollen allergy and nickel contact allergy, who developed four keloids on her back, spontaneously [24]. It is also relevant to emphasize the importance of not forgetting connective tissue disorders such as keloid scleroderma [25] and nephrogenic systemic fibrosis [26], both associated with keloid-like lesions, which can confuse and delay the diagnosis of these pathologies.

Some articles also described multiple cases of idiopathic keloids in individuals without an existing medical condition (Table 2). Within these, there were cases of keloids that have grown in the most common body areas, but also in the labia majora, post-auricular

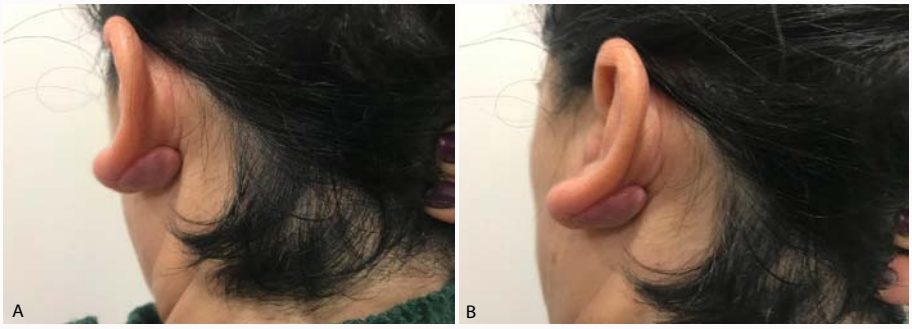

Figure 1: (A and B) Idiopathic posterior left ear keloid before treatment.

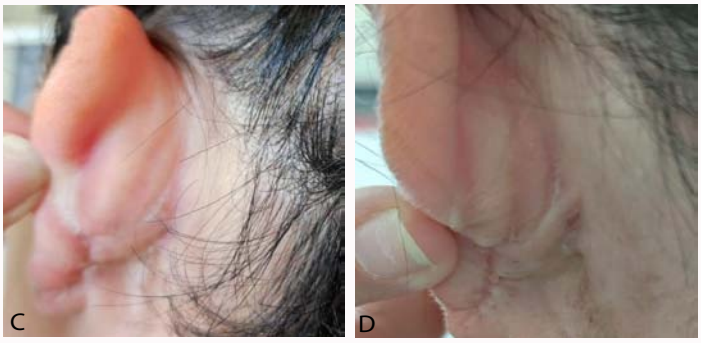

Figure 1: (C and D) 3 months following the procedure, the patient showed no evidence of recurrence and minimal hyperpigmentation.

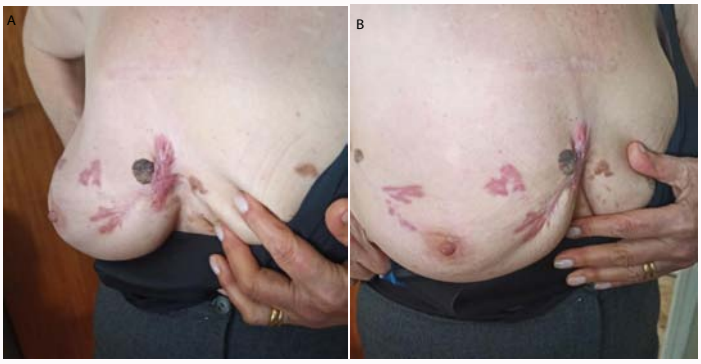

Figure 2: (A and B) Spontaneous thoracic keloids with no desire for surgery.

region, cornea and below the nipple.

An observational case-control study involving 259 Syrian individuals with keloids showed that 34 of them developed keloids spontaneously, mostly on the shoulders and the presternal region. Moreover, it also revealed a statistically significant association between these and blood group type A [34]. Another observational case-control study involving 88 Iraqi patients with keloids revealed that 34% of them had no history of trauma, and grew mostly solitary and on the upper body [35].

Therapies used

Regarding the different types of therapies, the use of various treatment methodologies was evident, from surgical excision in monotherapy or combined with postoperative radiotherapy, intralesional injections of corticosteroids, cryotherapy, silicone gel and occlusive dressings. As corroborated by existing knowledge, none of these therapies has yet demonstrated a fully proven success, as keloids are highly refractory to current therapies, with high recurrence rates.

However, and although little information is available on the cases examined, it was possible to verify different efficacy rates between the treatments used. The use of low dose UVA-1 phototherapy showed a reduction of itching and discomfort, flattening and softening of keloids, although it did not cause aesthetic or erythema improvement [27]. Despite this, an aesthetic and symptom improvement was seen in one patient after surgical excision followed by electron beam radiotherapy with a dose of 9 Gy [28]. Note that, although uncommon, there were no signs of recurrence six months after surgical excision of the post-auricular keloid used as monotherapy [29].

In one patient, the use of surgical excision followed by radiotherapy accompanied by compression techniques showed a slight recurrence after three months. Subsequently, intralesional Triamcinolone Acetonide was used with only partially satisfactory

result, with atrophy of half the lesions and partial regression of the other half [32]. In the same patient, the use of surgical excision in other lesions followed by intralesional injection of Triamcinolone Acetonide and radiotherapy showed no signs of recurrence after three years of follow-up [32]. In the remaining cases, the use of surgical excision in monotherapy [10], local radiotherapy alone [12,20], intralesional and local corticosteroid injection [13,15,20], cryotherapy [17] and silicone gel have not demonstrated therapeutic success [31].

It is important to note that rare cases of keloids that regressed spontaneously and relatively quickly (five years after their onset) with no signs of recurrence afterwards have been described [36,37]. Therefore, these articles provide encouraging knowledge regarding a possible cure of this pathology.

In the following, 2 reported cases of idiopathic keloids that have not yet been published in the literature will be presented.

Case 1

A 54-year-old Caucasian female with an idiopathic keloid in the posterior region of the left auricle underwent surgical excision followed by radiation therapy after two previous unsuccessful removal attempts (Figure 1A, 1B). Three months following the procedure, the patient showed no evidence of recurrence and minimal hyperpigmentation (Figure 1C, 1D).

Case 2

A 82-year-old Caucasian female developed several spontaneous thoracic keloids with no history of surgery or trauma. Patient did not want surgical excision (Figure 2A, 2B).

Discussion

As far as genetic syndromes are concerned, there are some possible explanations that try to justify their relationship with the emergence of idiopathic keloids. About corneal connective dystrophy, there seems to be a congenital defect capable of affecting some growth factors and, consequently, causing a dysregulation of connective tissue growth [12]. In turn, in the Filamin A G1576R Mutation Syndrome, the reason for the appearance of keloids may be due to a disturbance of the TFB-β signaling, which has been proven to be overregulated in these scars [13]. In Rubinstein-Taybi Syndrome, there are mutations in CREBBP, which is a co-activator of the Sma and Mad protein. These, once activated, also have a regulatory role in the activation of TGF-β [38]. In turn, in Dupuytren's contracture there is an accumulation of type III collagen, which is also present in keloids, favoring a possible common molecular origin [15]. Patients with Bethlehem myopathy show mutations in type VI collagen, which is important for skin integrity, wound healing and tissue repair. Therefore, changes in this collagen subtype appear to alter the structure of collagen, making the skin more susceptible to keloid formation [39].

The immune system plays a key role in the normal healing of the skin, but also in abnormal healing processes, such as keloids. These have a high number of mast cells, with a high concentration of histamine and consequent elevation of Immunoglobulin E. It is, therefore, interesting to note that patients with keloid scars are more likely to have allergic symptoms and vice versa [24].

Keloid scarring occurs due to excessive deposition of extracellular matrix in the skin, being the major constituent involved collagen produced by fibroblasts. Any skin lesion can lead to the activation of these cells through multiple cytokines and growth factors such as TGF-β, PDGF, VEGF, IL-6, TNF-α, INF-β, among others [40]. The continuous activation of fibroblasts and, consequently, an increase in the amount of collagen, leads to the growth of the keloid, which will only be resolved with the removal of this fibrotic tissue.

The drugs that can currently be used are based on three main principles. If we look at keloids as localized tumors, chemotherapy can be used (the most commonly used agents being Bleomycin, 5-Fluorouracil, and Mitomycin) [8]. In turn, if keloids are seen as inflammatory lesions, corticosteroids can be used (with Triamcinolone Acetonide being applied more frequently) and botulinum toxin A [8]. In addition, there also appears to be benefit with some systemic therapies such as those used for hypertension and treatment of breast cancer [8]. Some immunotherapies (such as Tacrolimus, Imiquimod, and Interferons) and volume-reducing therapies (such as intralesional collagenase injections) have been clinically tested, and genetic, epigenetic, and stem cell-based therapies are also in preclinical phase.

It should be noted that corticosteroid injections are often used as first-line therapy in the treatment of keloids, with a response rate varying between 50% to 100% and a recurrence rate between 9% to 50% [41,42]. However, they may have some adverse effects such as pain, hypo or hyperpigmentation, skin atrophy and telangiectasias [8].

Several studies have shown that surgical excision used as monotherapy is associated with a high recurrence rate, which can vary between 50% to 80%, and should be mostly avoided [43].

In order to reduce complications and refractoriness of the lesions, the use of a combination therapy with postoperative radiotherapy is currently advocated, preferably using electron beam radiation [8,43]. There is no universally accepted dose for the treatment of keloids, and a dose-dependent protocol should always be used on the most appropriate body area. In benign diseases, studies show that an intermediate dose of radiotherapy (between 3 Gy to 50 Gy, with an average of approximately 20 Gy) can be effective, with minimal or rare adverse effects [44]. A retrospective study analyzed 124 patients with 250 keloids who were treated with postoperative radiotherapy and showed that after a median follow-up period of 40 months the overall recurrence rate for all lesions was 5.6% [41]. The group of patients with lesions treated with 20 Gy had a recurrence rate of 1.6% while the group treated with <20 Gy had 9.6% (with an odds ratio of 0.16 (confidence interval 0.036-0.75, P=0.02) [41].

The cutaneous complications of radiotherapy (such as erythema, atrophy and telangiectasia) should be minimized by protecting more sensitive organs such as the thyroid and mammary glands [8], and in individuals aged <20 years, due to greater radiosensitivity, this should be avoided [43]. It should also be noted that the risk of radiation-induced cancer should not be overlooked, which, despite being very small, must be taken into account [44].

In summary, it is evident that idiopathic keloids are an extremely rare condition in which it is often difficult to determine its exact etiology due to the lack of relationship with any traumatic or medical condition. However, in certain cases, it is possible to attribute them to certain genetic syndromes, which shows a possible genetic influence on the origin of this type of scar. Regarding treatment, despite the numerous existing and developing therapies, keloids remain a condition that is highly refractory to therapy, and nowadays a combination of surgery and postoperative radiotherapy is advocated,

and the risks and benefits of its use should always be very carefully considered.

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