



American Journal of Dermatological Research and Reviews (ISSN:2638-1893)



DIFERENTIAL DIAGNOSES OF ANGIOKERATOMAS

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ABSTRACT

Angiokeratomas (AK) are probably the vascular lesions that induce more confusion in the literature. The most accepted classification of AK was performed by Imperial and Helwig^[1], and they divide these lesions into five classical types: Mibelli's AK, Fordyce's AK, corporis diffusum AK, circumscribed naeviforme AK and solitary or multiple acquired angiokeratomas. Nevertheless, in the clinical practice, is not unusual to see AK type lesions associated to different types of vascular anomalies, and these lesions have difficult handling.

In ISSVA classification AKs have been included as vascular anomalies provisionally unclassified.

We perform the differential diagnoses of AKs and according to clinical picture, histopathological aspect, immunohistochemical markers and radiological findings proposed to divide AKs mainly in two groups.

Primary AKs are the classical types. The new immunohistochemical findings suggest that these lesions might be included as mixed capillary-lymphatic malformations.

Secondary AKs are related with different vascular anomalies, secondary to other process with lymphatic obstruction, related to drugs, or associated with no vascular lesions as lymphoid lesions.

Different underlying vascular anomalies might be related with AKs including deep capillary-lymphatic malformations (CLM), venous-lymphatic malformations (VLM), capillary-lymphatic-venous malformations (CLVM) (Klippel-Trenaunay Sd), deep lymphatic malformations (LM), venous malformations (VM) as hyperkeratotic venous malformation, cavernomatous cerebral malformations, traumatic arteriovenous fistula and eccrine angiokeratomatous hamartoma.

Clinical aspect, radiological studies and histopathological examination might help to do a correct diagnosis of this heterogeneous entity.

Keywords: Angiokeratomas; Vascular lesions

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How to cite this article:

Jesús del Pozo, Felipe Sacristán, Manuel Gómez Tellado, Servicios de Dermatología, Anatomía Patológica, Cirugía Pediátrica. DIFERENTIAL DIAGNOSES OF ANGIOKERATOMAS. American Journal of Dermatological Research and Reviews, 2020; 3:34.

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INTRODUCTION

Angiokeratomas (AK) are probably the vascular lesions that induce more confusion in the literature. In the last classification of vascular anomalies performed in the International Society for Study of Vascular anomalies (ISSVA) meeting of Amsterdam (2018), these lesions and verrucous haemangioma have been included as vascular anomalies provisionally unclassified.

Etymologically, the word angiokeratoma has Greek origin, *Angeion-keras* + *oma*: vessels + horn + tumour [2]. Thus, angiokeratomas are lesions presented as red-violaceous to black papules with verrucous surface and, in the histopathological study, vascular ectasia located in papillary dermis with epidermal hyperplasia and marked hyperkeratosis.

The suffix "oma" is referred to tumour lesions, but since it has been shown that many of these lesions are not of tumour origin but malformative, the name seems to be inadequate.

Requena and cols [2] suggested that since the term angiokeratoma has been generically applied, it is preferable to restrict the designation angiokeratoma for the acquired hyperkeratotic vascular lesions resulting from ectasia of pre-existing blood vessels of papillary dermis.

The most accepted classification of angiokeratomas was performed by Imperial and Helwig [4], and they divide these lesions into five classical types: Mibelli's AK, Fordyce's AK, *corporis diffusum* AK, circumscribed naeviforme AK and solitary or multiple acquired angiokeratomas.

Nevertheless, in the clinical practice, is not unusual to see AK type lesions associated to different types of vascular anomalies, and these lesions have difficult handling.

In the old ISSVA classification, AKs but nor verrucous hemangioma, were included in capillary malformations. Nevertheless, three important studies have been recently performed about the origin of angiokeratomas and verrucous haemangioma.

Wang L et al [5] performed a study of lymphatic markers in 15 cases of AK corporis diffusum, 10 cases de Fordyce's AK, 10 cases of Mibelli's AK, and 10 cases of solitary AK. All lesions were positive to PROX-1, a marker of immature lymphatic vessels expressed in early lymphangiogenesis, before than D2-40, podoplanin. The authors suggest the lymphatic origin of classic AK.

Trindade et al [6] study 14 cases of children AK and confirm in all of them the presence of lymphatic markers, podoplanin, PROX-1 and ERG1. Since not all vessels were positive to lymphatic markers, the authors proposed the possible mixed component of AK, both capillary and lymphatic.

Couto AP et al [7] showed a somatic MAP3K3 mutation in 10 cases of verrucous hemangioma. Since this mutation confirms the venous origin of these lesions, the authors named this entity as verrucous venous malformation.

According to clinical picture, histopathological aspect, immunohistochemical markers and radiological findings, we propose a new classification of angiokeratomas shown in table 1.

TABLE 1 CLASSIFICATION OF ANGIOKERATOMA TYPE LESIONS

Primary angiokeratomas (True angiokeratomas, superficial capillary-lymphatic malformations).
1. Mibelli's AK: Acral lesions associated with cold exposure
1.1 Fordyce's: in genital area usually by venous hyperpressure
1.2 " <i>Angioqueratoma corporis diffusum</i> ":
1.2.1 Anderson Fabry disease
1.2.2 Other metabolic genetic defects
1.2.3 Without enzymatic alterations
1.3 Circumscribed naeviforme AK: nevoid lesions that begin early in life
1.4 Solitary or multiple AK
2. Secondary AK.
2.1 Lesions AK type as manifestation of other underlying vascular anomalies
2.1.1 Capillary-lymphatic malformations (CLM)
2.1.2 Venous-lymphatic malformations (VLM)

- 2.1.3 Capillary-lymphatic-venous malformations (CLVM) (Klippel-Trenaunay Sd)
- 2.1.4 Deep lymphatic malformations (LM)
- 2.1.5 Venous malformations (VM). Hyperkeratotic venous malformation
- 2.1.6 (Cavernomatous cerebral malformations. In 12% of cases presented with hyperkeratotic vascular lesions AK type
- 2.1.7 Traumatic arteriovenous fistula
- 2.1.8 Eccrine angiokeratomatous hamartoma (EAKH)
- 2.2 Secondary to other process with lymphatic obstruction
- 2.2.1 AK associated with lichen sclerosus, scars
- 2.3 Induce by drugs
- 2.4 others: APACHE

Classic types of AK might be classified as primary types but if these lesions accompany other usually deeper vascular malformations, they must be classified as secondary AK.

1. MIBELLI'S AK

Angiokeratoma was originally reported by Bazin in 1862, but the first characterized type with histopathological study was performed by Mibelli ^[8]

(1889) on a 14-year-old girl with erythema perniun.

Usually Mibelli's AK are acquired, papular, multiple lesions with acral distribution (fingers, toes, buttocks, knees, or earplugs), and they are related to ischemia in distal areas ^[9,10] (Figure 1). Nevertheless, congenital forms have been described ^[8].



Figure 1

These lesions are usually asymptomatic, although ulcerations have also been reported ^[9].

The condition that mainly occurs in female patients tends to be preceded by a long history of chilblains and acrocyanosis and several cases were associated with connectivopathies ^[11].

It is therefore likely that the ischemia that induces neoangiogenesis may be a factor favoring this form of AK, although its low frequency guides to other factors necessary for the development of these lesions.

Wang et al ^[4] in the histopathologic examination of 10 cases of Mibelli's AK showed dilated

vessels on papillary dermis with hyperkeratosis and epidermal hyperplasia. These vessels were negative staining for D2-40 and positive with nuclear staining Prox1. Prox-1 is superior to D2-40 in identifying endothelial cells of lymphatic malformations ^[12], but, in all cases, a variable number of vessels were negative, thus suggesting capillary origin. In this way and according to Trinidad et al ^[5] Mibelli's AK can be classified as capillary-lymphatic origin.

This form of AK, or at least the predisposition to suffer them, seems inherited in dominant autosomic mode with variable penetrance ^[13].

Several types of laser devices have been shown to be effective in the treatment of Mibelli's AK including pulsed dye laser (PDL), Nd:YAG laser, and sequential PDL-Nd:YAG laser^[14,15].

2. FORDYCE'S AK

Fordyce's AK are the second type of AK described in 1896 in a 60-year-old man with

bilateral varicocele. They are typically acquired, asymptomatic, 2- to 5-mm, dark red-to-black papules with a scaly surface located on the scrotum, shaft of penis, labia majora, or inner thigh (Figure 2). Congenital cases are also described^[16].



Figure 2

The precise incidence of angiokeratomas of Fordyce is unknown, but they are considered more common in men than in women of all ages. Sadowsky LM^[17] et al study the prevalence of genal AK in adult women and man. They concluded that this lesion is relatively common and much more frequent in mens.

The pathophysiology of Fordyce's AK remains unknown, although it has been proposed that an increase in venous pressure may contribute to their formation. Cases with response to surgical treatment of varicocele, venous traumatism or hernia have been described^[18]. But in others cases no antecedents of venous overpressure have been related.

Buehler S et al^[19] reported a case of scrotum AK associated with eyelid lesions. Both skin types show subcutaneous connective tissue that almost completely lacks adipose tissue and both are supported by muscufibrous structures, which lie underneath them. The authors suggest that disturbances in the supportive structures of the vessels at both sites caused patient's angiokeratomas.

Other cases of Fordyce's AK with associate lesions of AK in extragenital areas have been described^[20]. Also, it may be a manifestation of Fabry's disease^[21], and unilateral cases have been reported^[22].

It is important to differentiate Fordyce's AK of lymphangiectasias of scrotum, with or without venous communication, which are always related to lymphatic obstruction. When treated lymphangiectasias a clear liquid of lymphatic origin appeared, when treating Fordyce's AK a more or less profuse bleeding will develop.

Angiokeratomas are characterized by ecstasic capillaries in papillary dermis and acanthotic and hyperkeratotic epidermis. In the 11 cases of Wang et al^[4], all lesions were positive to D2-40 and negative to Prox-1. They are similar to previously described Fordyce's AK and can be classified as capillary-lymphatic malformations.

The papules of angiokeratoma of Fordyce are benign and asymptomatic, although they may bleed if traumatized, during intercourse, or from scratching. They do not usually require treatment, but if treatment is needed, locally

destructive methods, including laser [23,24,25,26,27], electrocoagulation, excision, sclerosis [28] or cryotherapy, may be used.

3. “ANGIOQUERATOMA CORPORIS DIFFUSUM” (AKD)

This type of diffuse AK that affects important areas of the body surface was described by Anderson and Fabry in 1898, and associated with alfa-galactosidase A deficiency. Afterwards other enzymatic defects have been associated with AKD [29,30,31,32] and cases of AKD without any enzymatic associated defects have appeared [33]. There are also cases of AKD associated with arteriovenous fistulas in lower limbs [34] and associated with tuberous sclerosis [35].

But the presence of AK in Fabry’s disease is very variable, some cases had multiple and numerous lesions, other a few numbers of AKs, other were presented without AK, and some cases had vascular lesions different to AK as telangiectatic lesions or capillary acquired haemangiomas [36].

In atypical cases, the diagnosis of Fabry’s disease was usually performed by the genetic studies in patients with hypertrophic cardiomyopathy.

They are also usually small but extremely numerous, asymptomatic lesions (Figure 3).



Figure 3

The histopathological examination of AKD are similar to Mibelli’s and Fordyce’s AK with dilation vessels on papillary dermis and a hypertrophic epidermis. In initial lesions the hypertrophic component is less evident. The definitive diagnosis of Fabry’s disease is made with the electronic microscopy findings, by the presence of melina-like inclusions or zebra bodies in the endothelial cells.

In the cases of Wang et al [4], 11 of 15 cases were positive for D2-40, and all of 15 cases positive for PROX-1. But between positive vessels with lymphatic markers these lesions present negative vessels. This support the opinion of Trindade F et al [5] about the capillary-lymphatic mixed origin of these lesions.

With the presence of multiple AK, a careful medical history is necessary, in order to perform genetic studies and rule-out Fabry’s disease. The cases of acquired AK without enzymatic defects might be consider in the last group, acquired multiple AK.

Currently substitutive treatment is available [37], and these lesions disappear or decreased drastically.

4. CIRCUMSCRIPTUM NEVIFORM ANGIOKERATOMA (CNA)

This variant of AK was described by Fabry in 1915 in opposition to generalized forms of AKD, to designate a form of AK that appeared in a localized form and was not accompanied by enzymatic defects. Fabry described the first case in a

11 year-old-women with lesions located linearly on thighs and buttocks that appeared at 7 years of age.

Dammert K ^[38] in 1965 described four new patients and review all previously reported cases of CNA. Two of this case were acquired and too congenital.

It is the least frequent one among the five types of the angiokeratomas and no other form of angiokeratomas has created as much confusion in the literature as this entity. This fact is probably due to the no existence of adequate criteria to define this variant of AK.

It has received many names throughout history, and several cases published as AK circumscriptum are not really this entity. They have been described associated with hemihypertrophy ^[39], "Caviar spots" on the tongue ^[40], Cobb syndrome ^[41], Klippel-Trenaunay syndrome ^[35], nevus flammeus ^[35], venous malformations ^[42] and

traumatic arteriovenous fistula ^[43]. It is one more example of the confusion that exists with these lesions because probably in all these associations, the diagnosis of neviform circumscribed angiokeratoma is incorrect. All these associations should be included within the AKs that accompany other vascular malformations or secondary AKs.

CNA represents a congenital, well-circumscribed area of vascular lesions that usually occur sporadically. A slight predominance in females have been described. The most common lesions involve the legs in a unilateral ^[44] or otherwise asymmetrical distribution but involvement of the trunk and other locations may also be present. The lesions often remain localized to small areas measuring some centimeters in diameter.

However, several very extensive lesions covering as much as one quarter of the body have also been reported. (Figure 4).



Figure 4

CNA represents a mosaic phenotype. Bechara et al ^[45] recommend using a neutral term like "segmental arrangement" that can be applied to various forms of cutaneous mosaicism such as the lines of Blaschko, the checkerboard pattern, or the lateralization pattern. The underlying mutation is so far unknown, but it will certainly turn out to be autosomal, because angiokeratoma circumscriptum has never been observed to be transmitted from a mother to her daughter. The histopathologic examination revealed dilated vessels in papillary dermis with different degrees of hyperkeratotic epidermis, similar to

other forms of classic AK. There is no involvement of the deep dermis and hypodermis. In the series of patients of Wang et al ^[4] and Trinidad et al ^[5] no cases of this entity were reported. In our cases the immunohistochemical pattern of CNA showed D2-40, GLUT-1 and WT1 negatives. No studies with LIVE-1 or PROX-1 have been performed in CAN in our knowledge.

The main differential diagnoses of CNA are the verrucous hemangioma ^[46], the level of confusion is such that recent works present both entities as synonyms^[47]. The main differential diagnosis data are summarized in Table 2.

TABLE 2 "ANGIOQUERATOMA CORPORIS DIFFUSUM"

1. Anderson-Fabry disease (X-L): α -galactosidase A
2. Sialidosis (AR): Sialidase
3. Galactosialidosis (AR):
 β -galactosidase and neuraminidase
4. Fucosidosis (AR): α -fucosidase
5. Aspartylglycosaminuria (AR): aspartylglycosaminidase
6. Kanzaki disease (AR):
 α -N-Acetylgalactosaminidase
7. β -mannosidosis (AR): β -mannosidase
8. GM1 Gangliosidosis (AR): β -galactosidase
9. D-2-hydroxyglutaric aciduria with enchondromatosis
10. Acid sphingomyelinase deficiency
11. Familiar form without enzymatic defects
12. Sporadic form without enzymatic defects
13. Disseminated form without enzymatic defects associated with arteriovenous fistulas and autosomal dominant inheritance
14. Associated to tuberous sclerosis

Several laser systems have been used to treat circumscribed angiokeratomas, including argon laser, carbon-dioxide laser, Cooper vapor laser, neodymium: yttrium-aluminum-garnet (Nd:YAG) laser, pulsed dye laser, alexandrite laser and intense pulse light source systems [48].

In summary, neviform circumscribed angiokeratoma is an acquired or congenital lesion, of superficial vessels, with segmental distribution that is not associated with other vascular malformations and has no deep involvement. It is probably a segmental form of Fabry's disease although there is no study that demonstrates it in a reliable way, probably because of the rarity with which this entity presents itself.

5. SOLITARY OR MULTIPLE ACQUIRED AK

This type of AKs was described by Imperial and Helwig [3] in 1967 in their classic classification of AK.

Among these five types of angiokeratomas, acquired angiokeratomas are the most common. These lesions are presented as small, warty, black, well-circumscribed papules that coalesce forming a plaque (solitary AK) (Figure 5) or appeared as multiple small lesions not associated with any enzymatic defects (Figure 6).

This form of AKs represents an acquired sporadic disorder rather than a developmental anomaly.



Figure 5

Multiple acquired AK are lesions with an aspect very similar to AKD, but probably less in number. In these cases, it is necessary to exclude

Fabry's disease. Some cases of these lesions are described in tongue^[3], in isolation or associated with other skin lesions.



Figure 6



Figure 7

Solitary acquired AK is a not rare entity that can be mistaken clinically for melanocytic nevus, malignant melanoma, verruca vulgaris, hemangioma, capillary aneurysm, Spitz nevus, focal epithelial hyperplasia or targetoid hemosiderotic hemangioma (Hobnail hemangjoma)^[3]. The excisional biopsy with meticulous histologic examination is important to confirm the diagnosis. Several forms of solitary AK are described in precise locations as tongue^[51,52], oral mucosa^[53], palmo-plantar^[54], vulvar^[55], subungal^[56], etc ...

Probably several lesions described as AK circumscriptum of the tongue^[57] are really solitary AK.

Wang et al^[52] studied 21 cases of solitary palmo-plantar AK and related these lesions with traumas. All cases were D2-40 negatives but no other lymphatic markers as LIVE-1 or PROX-1 were performed.

Histopathological examination revealed different levels of dilated vessels in papillary dermis, without deep involvement, accompanied by an acantotic and hyperkeratotic epidermis, in some occasions with true horn aspect.

In classic classification of AK this group is entitled as solitary or multiple AK with onset in adult life. This name is not adequate because several cases of this lesions are present in pediatric age.

In this manner, Prindaville B et al ^[58] study 22 cases of solitary AK in pediatric age. All 22 cases showed at least focal staining for Prox-1 and 21 (95%) demonstrated at least focal staining for D2-40, indicating a lymphatic immunophenotype in some vessels in each lesion.

Similar to described with the other classic forms of AK, probably these lesions should be considered as mixed vascular malformations, capillary-lymphatic malformations.

6. AK TYPE LESIONS AS A MANIFESTATION OF OTHER UNDERLYING VASCULAR ANOMALIES

There are many cases of vascular lesions clinically known as angiokeratomas that are part or are associated with vascular malformations of different nature. These lesions usually have deep involvement in opposition to classic types described previously. In these cases, both the imaging tests and the histopathological study can help us reach a correct diagnosis.

6.1 Capillary-lymphatic malformations

In some cases, within a capillary malformation, usually a Port wine stain, appear some isolated lesions of small size, warty and much darker tonality (Figure 7). When these lesions appear, it is necessary to perform imaging studies to rule out deep involvement, since angiokeratomas usually represent the superficial part of a deep lymphatic malformation.

6.2 Venous-lymphatic malformations

Many vascular malformations have a mixed component. Those that have a venous and lymphatic component may present AK aspect. The tongue is a usual localization of this mixed malformations where they have received different names such as lingual hemangiolympangioma, circumscribed lingual lymphangioma, circumscribed angiokeratoma ^[59] etc ... (Figure 8). In the histopathological study they present a mixed vascular component, one D2-40 positive and other negative for lymphatic markers and its usual the involvement of deep structures.

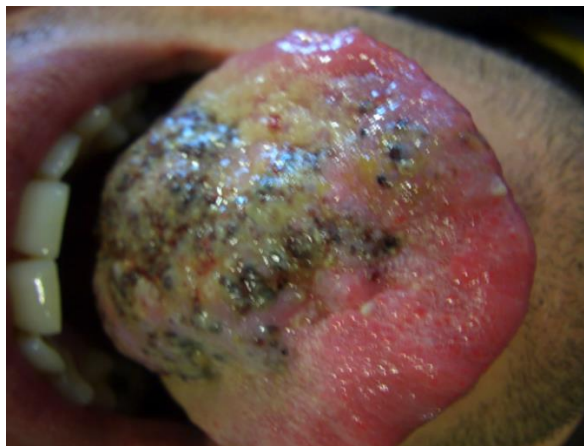


Figure 8



Figure 9

6.3 Capillary-lymphatic-venous malformations (Klippel-trenaunay Syndrome)

When a patient presents a capillary malformation, hemihypertrophy and a lymphatic and / or venous malformation, it is named as Klippel-Trenaunay syndrome. In these patients, the presence of lymphatic malformations usually manifests as angiokeratoma type lesions (Figure 9). It is very important to assess the presence of lymphatic lesions in patients with this syndrome since they are usually associated with a very aggressive course and worse prognosis.

Similar lesions might be present in complex syndromes with lymphatic component as CLOVES syndrome.

6.4 Lymphatic malformations

Within the great clinical expressivity of lymphatic malformations must be included angiokeratoma type lesions. These are usually located in the distal areas, and occur when the lymphatic dilations are superficial and induce the epidermal reaction that accompanies the angiokeratomas (Figure 10). When the lymphatic lesions are deeper, the cutaneous lesions that we most frequently encounter are lymphangiectasias.



Figure 10

6.5 Venous malformations

Pure venous malformations usually have a characteristic and monomorphic clinical appearance. Only in exceptional cases of blue rubber bleb naevus do they develop angiokeratoma type lesions.

In this group must be included the verrucous hemangioma currently named as hyperkeratotic venous malformation.

6.6 Cerebral cavernous malformations (CCM) associated with AK cutaneous lesions

In 1996, Ostlere et al ^[60] described a patient who presented cerebral and cutaneous hemangiomas associated with eruptive angiokeratomas. Probably it is the first description of cerebral cavernous malformations associated with cutaneous lesions.

Cerebral cavernous malformations (CCM), is a major cerebrovascular disease characterized by

abnormally elongated capillary lakes predisposing to seizures, focal neurological deficits, and intracerebral hemorrhages. The association of hyperkeratotic capillary malformations in relation to CCM is first described ^[61], but also the association with venous malformations ^[62], and other vascular malformations. Sirvente J et al ^[63] described a series of 417 patients with CCM, 9% presented cutaneous vascular malformations, 13 capillary malformations, 15 capillary-venous malformations of hyperkeratotic appearance, 8 venous malformations and 2 unclassifiable malformations.

Cerebral cavernous malformations can occur sporadically (80%) or family (20%). The family form presents an autosomal inheritance pattern dominant with a variable clinical penetrance. To date, 3 responsible genes have been identified CCM1 (KRIT1), CCM2 (MGC4607) and CCM3

(PDCD10), with more of 100 different mutations. The KRIT1 gene, detected in our 2 families, is the which is more frequently mutated in patients with skin lesions.

6.7 Traumatic arteriovenous fistula ^[64]

There is a case of angiokeratomas that occurred after the development of a traumatic arteriovenous fistula. It is also known that the lesions of the pseudo-kaposi type that accompany cases of arteriovenous fistulas or malformations have the appearance of angiokeratoma.

6.8 Eccrine angiokeratomatous hamartoma ^[65]

A lesion that met the clinicopathological criteria of eccrine angiomatous hamartoma and the surface of which showed features of angiokeratoma.

7. AK SECONDARY TO OTHER PROCESS WITH LYMPHATIC OBSTRUCTION

AKs secondary to process with lymphatic obstruction, mainly scars, may appear. In this manner, AK type lesions related to bullous epidermolysis scars ^[66], sclerodermatous graft versus host disease ^[67] or lichen sclerosis ^[68] (Figure 11) have been described.



Figure 11



Figure 12

Angiokeratoma-like changes in lichen sclerosis represent secondary features because of damage to the dermis by lichen sclerosis and are characterized histologically by ectatic thin-walled vascular spaces in the papillary dermis intimately associated with the epidermis.

8. AK INDUCED BY DRUGS

A group of these acquired multiple lesions have been associated with chronic trauma such as etanercept injection sites ^[69], or eruptively associated with enoxaparin treatment ^[70].

9. OTHERS

An entity clinically related to AK is the APACHE ^[71] ("acral pseudolymphomatous angiokeratoma

in children") but it really corresponds to a lymphoma. These lesions were initially described as isolated lesions, in acral areas in children, can simulate an angiokeratoma but the biopsy did not show a vascular lesion but a lesion of lymphoid origin.

10. VERRUCOUS HEMANGIOMA

The term of verrucous hemangioma was described by Imperial and Helwig [3] that defined its clinical—pathological characteristics and separated it from the rest of the angiokeratomas.

This entity has created an important confusion in the literature, and probably has not been designated with the best name [72]. Despite this, and due to its peculiar clinical and histopathological characteristics, probably it must be individualized [73].

Usually these lesions appear at birth or in the first years of life and in 95% of cases affect the lower extremities. They tend to be unilateral, although bilateral lesions have been described [74]. The size varies between centimeters to linear [75] or serpiginous lesions that affect an entire limb, and the presence of small satellite lesions is typical (Figure 12). The superficial warty mass is becoming much more marked over time, and bleeding episodes are common.

From a histological point of view, they initially present vascular dilatations located in the dermis and hypodermis. Over time the verrucous pattern with hyperkeratosis, papillomatosis and irregular acanthosis as well as the vascular

proliferation, becomes more evident, with very dilated capillaries accompanied by vascular spaces, lined by cavernous endothelium replete with blood, which dissect collagen fibers to the reticular dermis and subcutaneous fat. There may be inflammatory cells, hemosiderin and fibrosis in the papillary dermis and occasional vascular thrombosis. The deep part of the lesion may be connected or separated from the superficial part. Tennant LB et al [76] report that GLUT-1, the marker of infantile hemangiomas, is focally positive in verrucous hemangioma. Another study of 13 cases [77] shows that they cases are D2-40 negative, GLUT-1 positive diffuse in almost all cases WT1 positive. Wang et al [78] study 74 cases and concluded that VH is a vascular malformation with an incomplete lymphatic immunophenotype, as indicated by positive staining for Prox-1 and negative staining for WT-1 in the majority of instances.

Recently a genetic study of these lesions [6] showed a MAP3K3 mutation in 10 cases. This author named this entity as hyperkeratotic venous malformation. Nevertheless, no all tested cases were positives for the mutation and no other studies in other series have been performed.

At the moment probably, this entity might be classified as venous malformations.

The main differential diagnosis must be done with circumscribed neviform angiokeratoma, referred previously in table 3.

TABLE 3
CIRCUMSCRIPTUM NEVIFORM ANGIOKERATOMA (CNA) AND VERRUCOUS VENOUS MALFORMATION (VVM).
DIFERENTIAL DIAGNOSIS

	CNA	VVM
APPEARANCE	Adquired or congenital lesión	Usually congenital lesion
VERRUCOUS ASPECT	slight marked	very marked
BLEEDING	Unusual	Frequent
LOWER LIMB INVOLVEMENT	Unusual	The more frequent
VASCULAR ECTASIA	Superficial dermis	Superficial and deep dermis
VASCULAR PROLIFERATION	no	Yes
HYPERQUERATOSIS	Variable	Very marked
D2-40	Negative	Negative
GLUT-1	Negative	Positive
GENETIC STUDY	Not determined	MAP3CK

The treatment of these injuries in general is done in combination with laser and surgery [45]. In small lesions, the treatment of choice is surgery, but in large lesions, surgical treatment is accompanied by significant morbidity. In our experience, in these large lesions the combination of long-pulse CO₂ and Nd: YAG lasers can achieve excellent results with lower morbidity.

CONCLUSION

AK is a classic denomination of a vascular lesion with peculiar presentation that really correspond to several types of vascular malformations.

Clinical aspect, radiological studies and histopathological examination might help to do a correct diagnosis of this heterogenous entity.

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