

## Case Series

# Marginal acrokeratoderma: a case series

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**Received:** 09 June 2020

**Revised:** 08 August 2020

**Accepted:** 10 August 2020

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### ABSTRACT

Marginal acrokeratoderma (MAK) are complex disorders characterized by distribution of cornified papules/plaques along the dorso-plantar and dorso-palmar junction of the feet and hands. They belong to the family of punctate palmoplantar keratoderma. No associated gene defect has been detected. There are two clinically identical types of hereditary/familial MAK; namely acrokeratoelastoidosis (AKE) and focal acral hyperkeratosis (FAH); differentiated by the presence of elastorrhexis in AKE. The aim of this article is to report MPK lesions that are not included in the familiar groupings of punctate and polygonal papules. We described thirteen cases and reviewed the literature. Average age at presentation was 24 years, age ranged from 5 to 79 years. Majority of our cases had lesions on only their feet, that of FAH had lesions on only their hands and AKE had lesions on both hands and feet. Although most lesions reported in literature with FAH and AKE were characterized as 2-5mm flesh-colored to yellowish flat-topped/polygonal, keratotic/punctate papules, coalescing into plaques, we also reported lesions that were keratotic with cracks, desquamating and cobble-stone in appearance. This case series calls for more studies on variations in clinical presentation of MAK lesions and an opportunity to revisit the genetic basis and investigate triggers of this rare disorder.

**Keywords:** Marginal acrokeratoderma, Focal acral hyperkeratosis, Acrokeratoelastoidosis, Palmoplantar keratoderma, Punctate keratoderma

### INTRODUCTION

Marginal acrokeratoderma (MAK) are complex disorders characterized by the distribution of cornified and umbilicated papules/plaques along the dorso-plantar and dorso-palmar junction of the feet and hands respectively.<sup>1</sup> They belong to the family of palmoplantar keratodermas (PPK); which are heterogenous group of disorders featuring abnormal thickening of the palmar and plantar epidermis and includes genetic as well as acquired conditions. Clinically, hereditary PPK is generally classified as diffuse, striate, focal and punctate.<sup>2</sup> Punctate PPK is further categorized into punctate palmoplantar keratoderma type 1 (Buschke-Fisher-brauer type), filiform keratoderma, and MAK. There are two almost identical types of hereditary/familial MAK; namely acrokerato-

elastoidosis (AKE) and focal acral hyperkeratosis (FAH).<sup>3,4</sup> Both are characterized by multiple keratotic papules along the borders of the hands and feet with involvement of junctions of interdigital clefts and thickening of interphalangeal joints. FAH is histologically similar to AKE on hematoxylin and eosin staining. Whereas, further staining of the elastic tissue reveals normal findings in FAH, it shows decrease and fragmentation of elastin (elastorrhexis) in AKE.

Other disorders classified as MAK by Rongioletti et al include acrokeratosis verruciformis of Hopf, colloid milium, keratoelastoidosis marginalis of the hands, degenerative collagenous plaques of the hands, plane warts, digital papular calcific elastosis, mosaic acral keratosis and hereditary papulotranslucent acrokerato-

derma.<sup>1,5</sup> Acrokeratosis verruciformis of Hopf exhibits papillomatosis and ‘church spire configuration of the epidermis on histology. This is different from AKE and FAH, both reveal hyperkeratosis, hypergranulosis, mild acanthosis of the epidermis on histology. Colloid milium, keratoelastoidosis marginalis, degenerative collagenous plaques, digital papular calcific elastosis and plane warts, in contrast to FAH and AKE, all have known defined etiology (sun damage, chronic pressure and viral infection) and so are not considered as hereditary subtypes of MAK. Mosaic acral keratosis lesions are not located along the borders of the hands and feet and so not an appropriate differential of MAK. Hereditary papulotranslucent acrokeratoderma lesions are characteristically exacerbated after exposure to water. AKE was originally described by Costa while FAH was first introduced in 1983 by Dowd et al who reported fifteen cases.<sup>3,4</sup> Whereas, few authors consider the two as distinct entities, others have suggested that they are variants of the same disorder; variation being the result of inconstant genetic expression.<sup>1,6,7</sup>

We have noticed a handful of hereditary marginal acrokeratodermas that do not fit the morphological description of both Costa and Dowd et al.<sup>3,4</sup> After the eighteen cases of FAH reported by Dowd et al and Blum et al in 1983 and 1987 and few cases of AKE following Costa’s up until 1987, there have been a few MAK cases reported in the literature and mostly among Caucasians and Asians and rarely in Africans.<sup>1,3,8</sup> Review of these cases show some clinical deviations from those originally described and those seen in our dermatology clinic. We report thirteen cases of this rare entity in Nigerian patients who presented at the University of Abuja Teaching Hospital Gwagwalada in the last five years and review the literature; showing that keratotic lesions on the border junction of both hands and feet (MAK) do not necessarily have to be a group of punctate and polygonal papules.

**CASE SERIES**

We reviewed thirteen patients who presented with clinical features of hyperkeratotic thickening of the epidermis along the borders of the feet and hands of unknown etiology while undergoing dermatology consultation at the University of Abuja Teaching Hospital Gwagwalada, Nigeria. These cases were seen between January 2015 and 2020.

The characteristics of the patients are summarized in Table 1. There were seven males and six females, with a median age of 17 years (range 6-45 years old). They had varied occupation, from students/school children to tailor, trader, teacher, lawyer, military officer and housewife. The median duration between onset of lesions and presentation was 4 years (range 1-19 years). Patients had lesions affecting only feet, hands as well as feet and hands alone. Only 2 patients have family history of similar lesions. Regarding the morphology of the lesions on the borders of

the feet, four of the cases had multiple cracks with hyperkeratosis (Figure 1 b-d, j), three cases had desquamating lesions (Figure 1 f, i, k) and a patient presented with cobblestone appearance of polygonal hyperkeratotic papules/plaques (Figure 1 l). Lesions of three patients are described as hyperkeratotic plaques (Figure 1 e, g, h), one as polygonal papules (Figure 1 a) and one as crateriform papules (Figure 1 m). All the lesions except in five cases (Figure 1 a, b, i, l, m) were characterized as itchy while none of the patients had hyperhidrosis. The plantar surface was spared in all except in those with involvement of the junction of interdigital clefts and non-weight bearing arch of the foot. Examination of other parts of the body did not reveal any abnormalities. Review of systems were not contributory. No co-morbidities were associated with the disorder. Laboratory studies for full blood count, liver function tests and erythrocyte sedimentation rate disclosed normal values. Contact dermatitis was ruled out via patch tests using European baseline series. Histology of skin biopsy reported focal hyperorthokeratosis and acanthosis. No parakeratosis or infiltration of inflammatory cells was observed within the epidermis or dermis.

**Table 1: Characteristics of the thirteen cases series.**

Clinical parameters	Frequency
<b>Age: Mean±SD (years)</b>	23.3±15.1 (range 6-45)
<b>Male:Female</b>	7:6
<b>Occupation</b>	
Students/school children	7
Tailor	1
Trader	1
Teacher	1
Lawyer	1
Military officer	1
Housewife	1
<b>Duration of lesion before presentation Mean±SD (years)</b>	5.5±5.1 (range 1-19)
<b>Location of lesions</b>	
Hands only	1
Feet only	8
Hands and Feet	4
Relatives with similar lesions	2
<b>Description of lesions</b>	
Multiple cracks with hyperkeratosis	4
Desquamating lesions	3
Cobblestone appearance	1
Hyperkeratotic plaques	3
Polygonal papules	1
Crateriform papules	1

All the patients were managed with 20 to 30% salicylic ointment and highly potent corticosteroids creams with variable degree of response.



**Figure 1: Marginal acrokeratoderma of cases series; (a) skin-colored polygonal papules on hypothenar region, (b,c,d,j) lesions on marginal border of feet are multiple cracks of hyperkeratotic plaques, (f,i,k) lesions on marginal border of feet are desquamating plaques, (l) patient with cobblestone appearance of polygonal hyperkeratotic papules/plaques on marginal border of feet and punctate papules on both palms, (e,g,h) patients with hyperkeratotic plaques marginal border of feet, (m) patient with crateriform papules on both hands and feet.**

## DISCUSSION

Although, next generation sequencing has been used by recent studies to identify mutations in genes associated with PPK, these are yet to be fully defined in FAH and AKE.<sup>2,9</sup> In fact, diagnosis of PPK in resource poor settings, where molecular investigations are expensive and out of reach, can be achieved by recognizing the distinct clinical pattern and extent of palmoplantar involvement, pattern of inheritance, degree of mutilation, presence of additional dermatological and systemic associations, and histopathological features.<sup>2,9</sup> Diffuse PPK is noticed in infancy and characterized by uniform thickening of palms and soles, with or without a clear demarcation at the lateral aspects; and, contiguous expansion of hyperkeratosis to the dorsum, inner wrists and Achilles tendons (PPK with transgrediens). Some diffuse PPK can worsen or improve with age (progrediens).<sup>2,9</sup> Focal PPKs are defined by the presence of multiple and painful callosities formed mainly over pressure points and clinically manifests within the first 2 years of life. Striate PPK is characterized by linear hyperkeratotic lesions on the dorsal aspect of the hands and feet along corresponding tendons and friction-bearing areas. Some manifest in infancy, among manual workers

or in association with dilated cardiomyopathy.<sup>2,9</sup> Punctate PPKs are defined by multiple hyperkeratotic punctate papular lesions involving whole or part of palms and soles. Clinically, it manifests in late childhood to adulthood. Marginal papular acrokeratoderma is classified as a punctate PPK but with very little information.<sup>1,2,9</sup>

Since Dowd and Blum's initial description, slightly more than a dozen cases of FAH have been reported.<sup>1,5,10-20</sup> We reviewed thirteen cases in the literature (from 1996 to 2018). The patients were older with a median age of 35 years (range between 9 and 62 years old). Of note, only two of the thirteen cases were males.<sup>8,10</sup> Majority of the cases had long and ill-defined duration of onset. Four of the patients were dark-skin while eight were either Caucasians or Asians. Two of the cases had associated hyperhidrosis and three had a family history of similar lesions. Unlike in our series, hand involvement was seen in all except for one case who was identified as being African in origin.<sup>12</sup> Five cases had affection of both hands and feet. Lesions were mostly located on the dorso-palmar or dorso-plantar junction of the hands and feet and are generally described as multiple, 1-5 mm, yellow to skin-colored discrete, confluent and clustered papules



which sometimes coalesces to plaques. Associated comorbidities were quite few (dystrophic nails, hearing loss and carcinoid syndrome) otherwise patients were clinically normal. All the cases had histopathological report of lesions showing shallow depression of the epidermis with marked orthohyperkeratosis, no parakeratosis or any evidence of inflammation. Some cases reported normal elastic tissue using different staining methods.

Since 1990, slightly more than two dozen cases of AKE have been reported.<sup>6,7,21-40</sup> We reviewed twenty-four cases in the literature. The patients were also older with a median age of 36 years (range between 5 and 79 years old). Interestingly, only four of the cases were males.<sup>22,24,28,29</sup> The duration between onset of lesions and presentation was quite varied, two cases had the lesions present from birth, two presented within months of onset while eleven cases had less than 10-year history.<sup>6,21,22,24-31,34,39,40</sup> The ethnicity of eight cases was not given; however, African/dark-skin was reported in five of the remaining nineteen cases.<sup>6,26,31,35,40</sup> Family history was reported in only four cases.<sup>33-34,37,38</sup> Other co-morbidities include Crohn's disease, asthma and dystrophic nails.<sup>25,27,31,32</sup> Two cases reported a unilateral affectation; one on the left hand and foot and the other on right hand and foot respectively; in these cases, lesions were noticed at birth.<sup>30,31</sup> Fifteen cases had involvement of both hands and feet, six cases had involvement of only their hands while three cases had involvement of just their feet (Arabian, Japanese and African). The description of the lesions was as similarly reported in FAH cases above; 2-5 mm flesh-colored to yellowish flat-topped, keratotic papules, coalescing into plaques, distributed linearly along lateral and medial margins of the feet and hands. One case from India had lesions on the non-weight bearing arch of the foot while an African woman had lesions on her Achilles' tendon.<sup>6,37</sup> Histopathological documentation of all cases was similar to FAH while identification of decrease and fragmentation of elastic fibers was performed with Verhoeff's-van Gieson, acid orcein, aldehyde-fuchsin, Weigert staining and or electron microscopy.<sup>36</sup>

From the review of the literature and our patients, we attempted to compare the clinical pattern/morphology and extent of palmoplantar involvement. MAK is more common in females than males, though our cases had an almost equal distribution. The age range of patients was similar across the case series, FAH and AKE; however, the median age of our case was younger by half to those reported in FAH and AKE. There was a wide variation in the duration between disease onset and clinic presentation in reviewed cases and our patients, some spanning decades. The number of persons with family history of similar lesions was quite low across the three sets of cases. Although all cases reviewed and reported in this article had lesions on the border junction of the acral region, some differences in the location and morphology were noticed. While most of our patients had affectation of their feet alone, most patients with FAH had lesions present on only

their hands and most AKE patients had both hands and feet affected. Additionally, almost all of the lesions reported in the literature with FAH and AKE were characterized as 2-5mm flesh-colored to yellowish flat-topped, keratotic/crateriform polygonal papules, coalescing into plaques, we also observed some patients with lesions characterized by multiple cracks and hyperkeratosis affecting the non-weight bearing arch (sole of the toes and medial arch) of the feet.

In the article by Rongioletti et al where he suggested the term 'marginal papular acrokeratoderma' be used for 'several conditions sharing keratotic, usually crateriform papules along the borders of the hands and feet'; keratotic plaques with or without cracks and fissures along the borders of the hands and feet were not mentioned.<sup>1</sup> Also, the possibility that marginal acrokeratodermas can contiguously expand (transgrediens) and improve/worsen with age (progrediens) was not commented upon. Only, Liu et al reported plaques as a rare presentation of AKE.<sup>39</sup> As a matter of fact, four of our patients with MAK presented with keratotic plaques with cracks, three with desquamating plaques and one with cobblestone appearance. This possibly suggests that MAK lesions should not be strictly recognized as 'polygonal, flat-topped, crateriform papules'. Also, the involvement of the borders of toe digits and non-weight weight bearing arch of the plantar surface in most of our patients indicates the transgrediens nature of some MAK. These calls for more studies on the clinical presentation and genetic abnormalities associated with the epidermal changes of inherited MAK. The theory that MAK is a disorder resulting from variable genetic expression of dermal elastic tissue is still controversial; also, cases with associated systemic manifestations of elastic tissue disorder have not been reported and none was observed in this review.<sup>20</sup> Two strong limitations to our case series were the lack of elastic tissue staining and genetic study. This was due to paucity of technical knowledge. We hope to participate in collaborative study on genetic mutations of MAK in future.

## CONCLUSION

Unpublished report of PPKs from our dermatology clinic show a hospital-based prevalence of 1.06 per 100 cases (total 5371). Our cases revealed that MAK lesions can also include plaques, hyperkeratotic plaques, desquamating plaques and cobblestone appearance. Genetic study of MAK is needed for further understanding of this interesting group of palmoplantar keratodermas and will aid the development of effective treatment guidelines

## ACKNOWLEDGEMENTS

We wish to acknowledge the records department for assistance in the retrieval of medical records used in this article.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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**Cite this article as:** Ibekwe PU, Ogunbiyi AO. Marginal acrokeratoderma: a case series. *Int J Res Dermatol* 2020;6:670-5.