Case and Review

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Kerinokeratosis Papulosa of Childhood

Boris Bauer[a] Matthias Goebeler[a] Benedikt Weissbrich[b] Andreas Kerstan[a]

[a]Department of Dermatology, University Hospital of Würzburg, and [b]Institute of Virology and Immunobiology, University of Würzburg, Würzburg, Germany

Key Words
Kerinokeratosis papulosa · Waxy papulosis of childhood · Human papillomavirus · *EVER1* · *EVER2*

Abstract
Background: Kerinokeratosis papulosa (KP) is considered an extremely rare genodermatosis presenting usually as waxy papules on the trunk in childhood. ***Objective:*** To describe and analyze the clinical, histological and potential etiopathological aspects of KP. ***Methods:*** The dermatoscopic features of a new case of KP of childhood are investigated. The presence of human papillomavirus (HPV) DNA in lesional skin was studied by polymerase chain reaction. Furthermore, all cases of KP of childhood reported so far were reviewed. ***Results:*** As a diagnostic tool, we describe for the first time a dermatoscopic feature, namely a cribriform pattern of KP, in an 11-year-old boy. In addition, we detected HPV (type 57) in his KP lesions. ***Conclusions:*** Dermatoscopic examination might be a useful tool to distinguish KP from other skin lesions, e.g. common warts. The detection of HPV type 57 might hint to an etiological role of HPV for KP.

Introduction

Kerinokeratosis papulosa (KP) (from the Greek 'kerinos' = 'waxy') or 'waxy papulosis of childhood' was first described by Coleman et al. in 1994 [1], with only few reported cases since then [2–6]. Clinically it presents with multiple, usually non-symptomatic or mildly itching, non-follicular, small, flat, shiny papules distributed mostly on the trunk or proximal extremities. Since it frequently manifests shortly after birth or in early childhood and since cases with a segmental distribution have been reported, it is considered a genodermatosis with a presumed autosomal-dominant phenotype [2]. However, corresponding genes and the pathophysiology of the disease remain unknown so far.

On clinical grounds KP may easily be confused with a range of other skin conditions such as verrucae planae juveniles, mollusca contagiosa or seborrheic keratosis. To add a diagnostic tool we analyzed the dermatoscopic features of one case with KP and in addition focused on a potential role of human papillomavirus (HPV) infection.

Methods

HPV Genotyping

Polymerase chain reaction (PCR) amplification with consensus sequence primers and sequence analysis was carried out as described previously [7]. Briefly, formalin-fixed and paraffin-embedded samples were cut into 10-µm sections. Following deparaffinization, DNA was extracted from the samples using the Qiagen DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. PCR was carried out using the Qiagen Hot Star polymerase kit and the primers MY09, MY11 and HMB01 [8]. To confirm the sequence specificity and to determine the HPV type, PCR products of the expected size were sequenced completely in both directions using Big Dye terminator chemistry and the ABI Prism 3100 instrument (Applied Biosystems, Darmstadt, Germany). Obtained sequences were blasted against viral sequences in GenBank to determine the HPV type.

Case Report

An 11-year-old boy presented with 17 congregated yellow-brownish, flat, shiny papules with a waxy aspect on the right shoulder, which had developed over the last 2–3 months (fig. 1a). The lesions were asymptomatic, followed no clear segmentation and had no follicular connection. No erythema, scaling, verrucous surface or umbilication were present. Hair, nails and mucous membranes were unremarkable. His parents denied a family history of similar skin manifestations. Before his admission to our clinic, the papules had been unsuccessfully treated with cryotherapy under the diagnosis of mollusca contagiosa. He had been diagnosed with mental retardation most likely due to perinatal asphyxia in combination with attention deficit hyperactivity disorder. The patient had suffered from measles at the age of 1, mumps

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E-Mail karger@karger.com
www.karger.com/drm

Dr. Boris Bauer
Department of Dermatology, Venereology and Allergology
University Hospital Würzburg, Josef-Schneider-Strasse 2
DE–97080 Würzburg (Germany)
E-Mail Bauer_B1@ukw.de

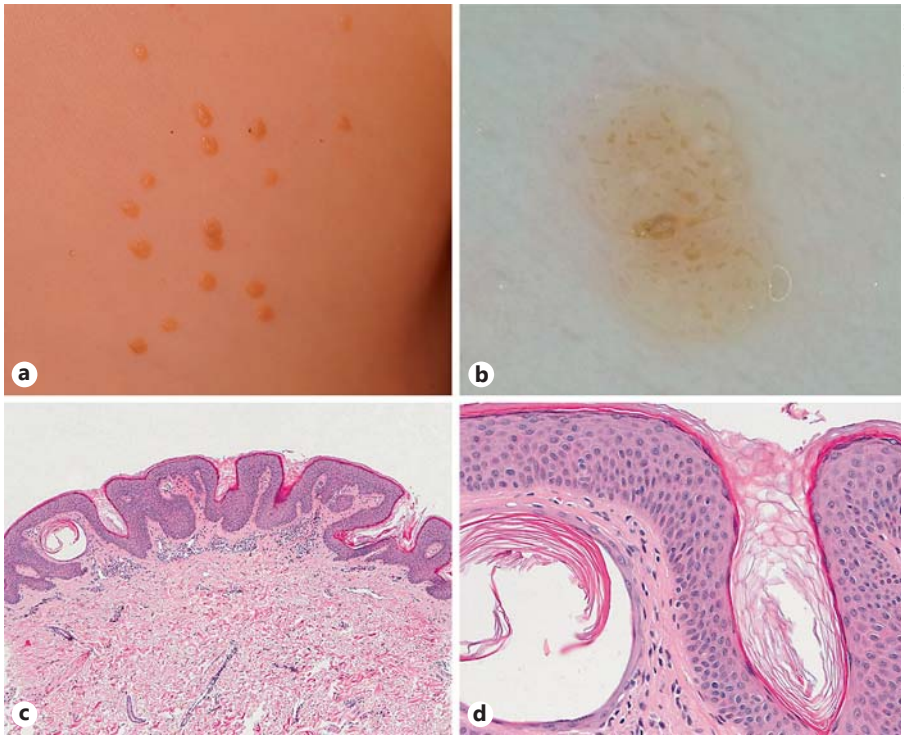

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Fig. 1. Clinical and dermatohistopathological presentation. **a** Multiple yellow-brownish, flat, shiny papules with a waxy aspect on the right shoulder. **b** Dermatoscopy with a cribriform pattern. **c**, **d** Histology showing acanthosis with mild hyperkeratosis accompanied by a mild superficial lymphocytic infiltrate. On the left border a small epidermoid cyst (milium) is seen. Hematoxylin and eosin. **c** ×40, **d** ×200.

at the age of 2 and rubeola at the age of 6. Furthermore, he had been hospitalized with severe pneumonia when 7 years old.

Dermatoscopy showed yellow papules with a translucent aspect and cribriform pattern, similar to a non-pigmented flat seborrheic keratosis without pseudocysts (fig. 1b). Histological examination of a papule (fig. 1c, d) revealed acanthosis with mild hyperkeratosis accompanied by a very mild superficial lymphocytic infiltrate, compatible with the histological criteria of KP reported in the literature [1]. The small epidermoid cyst on the border of the lesion presumably arose secondary to previous cryotherapy. As keratotic disorders may result from infection with HPV, histological samples were investigated for the presence of HPV DNA by PCR. Interestingly, sequencing of the PCR products yielded DNA of HPV type 57 (HPV-57), a HPV type which has been described to be prevalent in warts [9]. However, clinical, dermatoscopic and histological examination were not typical for verrucae vulgares or planae.

Discussion

Epidemiology and Clinical Presentation

KP is an extremely rare and potentially underreported disease which may easily be confused with a range of other skin conditions such as verrucae planae juveniles, mollusca contagiosa, seborrheic keratoses, Darier's disease or lichen amyloidosus. Since lesions are usually asymptomatic or only mildly itching, the prevalence of this entity might be much higher as affected patients do not suffer from discomfort and thus do not consult a physician. An association of KP with comorbidities could not be established so far.

As summarized in table 1, seven cases in children (including the presented case), mean age 9.0 ± 3.9 years, and two in adults, aged 56 and 63 years, respectively, have been reported so far, with a slight preponderance of females (female:male ratio 5:4). Histology exhibited acanthosis, papillomatosis and orthokeratotic hyperkeratosis in all reported cases as well as a mild dermal inflammatory reaction in some cases. Clinical features included flat, shiny, waxy papules usually located on the trunk or proximal extremities (table 1). The natural course of the disease is unknown; especially, it is unknown whether the papules regress over time or whether in adulthood they are mistaken for e.g. seborrheic keratoses.

Diagnosis

In their original description, Coleman et al. [1] pointed out distinct hallmarks to distinguish waxy papules of childhood from other forms of genetic filiform or papular hyperkeratoses, including multiple minute digitate hyperkeratoses, minute aggregate keratoses and disseminated spiky hyperkeratoses. To further distinguish KP from other possible differential diagnoses, Tan and Zhu [6] proposed six diagnostic criteria, listed in table 2. However, these criteria have not been evaluated, and most cases in the literature, including our own, do not match all of the proposed criteria. Furthermore, dermatoscopy has not yet been used to distinguish KP from other papulous disorders. In our case, a specific cribriform pattern reminiscent of seborrheic keratosis but without the typical pseudocysts was observed. As this is a distinct feature, we propose a cribriform pattern in dermatoscopy as a novel clue for the diagnosis of KP.

Genetics

KP has been considered to be a genodermatosis [3]. However, none of the cases found in the literature showed a positive family history, and only one case of waxy papules in two sisters has been described in the original publication [1]. In 2001, Mehrabi et al. [2] reported a case of waxy keratoses in a segmental distribution along one leg in an 11-year-old girl. As an explanation for the distribution the authors discussed the possibility of a mosaicism for a single gene disorder. This would hint to an autosomal-dominant inheritance pattern representing a type 1 segmental distribution according to the concepts of cutaneous mosaicism developed by Happle [10, 11]. In this case, a gonadal mosaicism in a parent would be responsible for the recurrence in the siblings reported in the first described case. Alternatively, a postzygotic 'second hit' with loss of heterozygosity for the normal allele and therefore a recessive inheritance has been discussed [2]. Interestingly,

Table 1. Demographic and clinical features of reported KP cases

Reference, year	Sex/age, years	Age at onset, years	Localization	Itching	Family history of waxy keratoses	HPV type	Associated morbidities
Reports in children							
Coleman et al. [1], 1994	F/5	3	trunk, proximal limbs	no	no	n.t.	none
	F/6	1	neck, trunk, limbs	yes	yes	n.t.	epilepsy, herpes zoster (age 4)
	F/7	2	upper arms, back	no	yes	n.t.	
Mehrabi et al. [2], 2001	F/11	1	right leg	no	no	n.t.	none
Happle et al. [3], 2004	F/7	4	face, upper arms, trunk, thighs	n.d.	no	n.t.	linear epidermal nevus
Gönül et al. [4], 2008	M/16	8	arms, legs	no	no	n.t.	none
This report, 2015	M/11	10	right scapula	no	no	57	mental retardation
Additional reports in adults							
Donati et al. [5], 2011	M/63	25	back, then spreading all over body	n.d.	no	6, 56, 66, 38	none
Tan and Zhu [6], 2013	M/56	55	dorsum of hands	yes	no	n.t.	n.d.

n.d. = Not described; n.t. = not tested.

Table 2. Proposed diagnostic principles, modified from [6]

i	uniform, non-follicular, shiny skin-colored to reddish papules
ii	usually asymptomatic, papules can be easily detached
iii	itching may be present
iv	the diameter of the papules usually exceeds their height
v	histologically lamellar and compact orthokeratosis, acanthosis and papillomatosis in which tenting of the epidermis and stratum granulosum may sometimes be pronounced
vi	histologically no obvious signs of spongiosis or inflammatory change in the dermis, no koilocytes
vii (proposed)	dermatoscopy shows cribriform pattern

Happle et al. [3] reported the case of a 7-year-old girl with KP distributed over the whole body in combination with a linear epidermal nevus on the left upper arm that histologically showed a conspicuous hyperkeratosis and acanthosis. In the context of a type 2 segmental manifestation the diffuse phenotype could be explained by heterozygosity for the underlying mutation and the linear nevus or 'nevus kerinokeratosus' would result from loss of heterozygosity at an early developmental stage [3].

As keratotic disorders can be the result of HPV infection, Donati et al. [5] tested a 63-year-old man with KP-like lesions for localized HPV infection. They also investigated epidermodysplasia verruciformis-associated mutations in the epidermodysplasia verruciformis endoplasmatic reticulum genes 1 and 2 *(EVER1* and *EVER2)*, which predispose for a higher susceptibility to beta-papillomavirus infection [5, 12, 13]. HPV is a double-stranded DNA virus of the Papillomaviridae family and the species are phylogenetically classified into the genera α, β, γ, μ and γ/ν [14]. Epidermodysplasia verruciformis represents a genodermatosis where infections with multiple different HPV types of the beta-papillomavirus type, especially HPV-5 and HPV-8, are a hallmark of disease. It presents with hyperkeratotic and flat reddish to yellow-brownish papules especially on the acral extremities and the face [12]. Although the authors detected common homozygous polymorphisms in *EVER2*, a clear connection to HPV-induced lesions failed since the vast majority of several skin biopsies obtained from different locations gave rise to alpha-papillomaviruses HPV-6, HPV-56 and HPV-66, while only one lesion was positive for the beta-papillomavirus HPV-38. Therefore, involvement of these genes in the pathogenesis of KP seems to be unlikely.

In line with this, we found alpha-papillomavirus HPV-57 DNA in one lesion of our patient. HPV-57 is frequently found in viral warts of children [9]. In a recent study performed in elementary schools in the Netherlands, HPV-57 DNA was detected in 14% of all warts. In contrast, in swabs taken from healthy skin in the same group, HPV-57 was a rare finding, although 80% of all tested children had at least one HPV-

positive non-wart swab [15]. In line with these results, HPV genotyping in future KP cases has to reveal whether detection of HPV DNA, especially HPV-57, is a common finding favoring the idea that KP might reflect a particular type of viral papilloma. Since HPV DNA is commonly found in unaffected skin, the additional detection of HPV RNA in lesional skin would further strengthen this concept.

However, on clinical, histological as well as dermatoscopic grounds, the lesions in our patient were clearly different from classical viral warts, including verrucae planae. On histology there were neither vacuolated keratinocytes (bird's eye cells) in the upper Malpighian layer nor detectable hypergranulosis, which both are typical signs for verrucae planae. Furthermore, localization on the trunk is most unusual for verrucae planae, which are usually distributed in areas exposed to UV light, including the face and back of the hands.

In summary, KP as reported here can be associated with a HPV infection, which might represent an etiological factor. Besides histology, dermatoscopic examination seems to be a useful tool to distinguish KP from common warts.

Disclosure Statement

The authors have no conflict of interest or funding sources to disclose.

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