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Letter to the Editor

Keratoacanthoma *vs.* squamous cell carcinoma in contrast with keratoacanthoma *is* squamous cell carcinoma

To the Editor

Forslund et al.[1] accept the premise that keratoacanthoma (KA) and cutaneous squamous cell carcinoma (SCC) are not within the same biological and diagnostic spectrum, in contrast with recent thinking by a number of authors, notably Ackerman, who regard solitary KA as a specific type of SCC.[2,3]

Forslund et al. state that 'Keratoacanthomas are benign, clinically distinct skin tumors generally located at sun-exposed sites in elderly fair-skinned people. . .Histologically, keratoacanthomas are diagnosed by their architecture as well as their cytological features, and when also considering their characteristic clinical history most keratoacanthomas can be distinguished from SCCs.' The authors do not state whether they believe KAs are examples of hyperplasia or neoplasia. This distinction, however, is important because hyperplasias are reversible conditions, whereas neoplasms, as a rule, do not resolve spontaneously.

To approach this issue another way, if one were to develop the hypothesis that KA is hyperplasia, rather than neoplasia of keratocytes, the finding of human papillomavirus (HPV) is an intriguing premise on which to base that investigation, as any dermatologist or dermatopathologist knows from dealing with verrucae vulgares. In order to investigate that question scientifically, one would, however, need to identify a control group of uncontroversial squamous carcinomas as part of any such study, in addition to the experimental group, i.e. KAs. Further-more, it would also be extremely useful to find examples of 'KAs' that metastasized (i.e. unequivocal SCCs that are well differentiated) and to subject these lesions to a study of a possible association with HPV.

In the study by Forslund et al., however, I do not see any evidence that they considered investigating controversial or uncontroversial cutaneous SCCs as a control group. Thus, how are the authors to know whether HPV might be detected in cutaneous SCCs? Furthermore, how would the authors respond to the advocates of KAs are squamous carcinomas? Those who include KAs as examples of SCCs would argue that some SCCs contain HPV, and, perhaps, that HPV is an inducer, not unlike HPV 16- and 18-associated SCCs that have been documented well in the literature. They might also argue it that it is not causal at all – true, true but unrelated. In contrast, the argument from those who believe that KA is hyperplasia would probably favor the point of view that HPV causes KA, which regresses once the effects of HPV have played out. However, without using control groups of well-documented examples that either camp would agree are KAs or SCCs, the presence of HPV in a KA has no scientific meaning whatsoever, at least regarding the question of KA vs. SCC in contrast with KA is SCC.

Finally, the authors did not show examples photographically of what they were investigating, thus the reader cannot tell whether these are classical KAs or classical SCCs.

I urge the authors to clarify their nosological position on KA and to show photographically what they mean by the use of that term.

Yours sincerely

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Response to the Letter

The authors are pleased to answer questions related to the above-mentioned and recently published article of ours and appreciate that our interest in the intriguing biology of keratoacanthomas (KA) is shared by others. Please find our answers to the issues raised in the letter.

We consider KA, like most textbooks of pathology, to be a benign keratinocytic neoplasm, based on the fact that it has a proliferative growth phase followed by a period of regression and often scarring. We agree that one may argue that this type of behavior could be labeled hyperplasia, but the general biological behavior of KA is very different from what is characteristic of malignant neoplastic growth. We therefore cannot find any reason to consider KA as a cutaneous squamous cell carcinoma (SCC), although there are reports claiming that KA has metastasized. KA has a distinct proliferative phase, and proliferation by itself is considered to be a carcinogenic event that may explain that KA exceptionally develops into SCC. These are exceptions confirming the rule. Our contention on this is supported by a recent review on the topic by D. Weedon.[1]

The present paper is the second one in our attempts to elucidate the particular biology of KA and is mainly based on lesions (Fig. 1) that are classified in detail in a previous publication that should be consulted.[2] Thus, only lesions with the typical architecture of KA were included, irrespective of features like infiltration and cellular atypia that in addition to estimated age and recorded age of the lesion were graded. We have thus related our findings in the present paper to these variables, without finding any statistical association between human papillomavirus (HPV) status and age of lesions, and cellular atypia and infiltration. We apologize for the fact that these results were not reported nor discussed in the present paper, where we only report that HPV is neither associated with young nor old age of lesions.

Besides trying to find out which genes and geneproducts that are involved in the development and particularly in the regression of KA, it is of major interest to find markers that distinguish KA from SCC (Fig. 2).

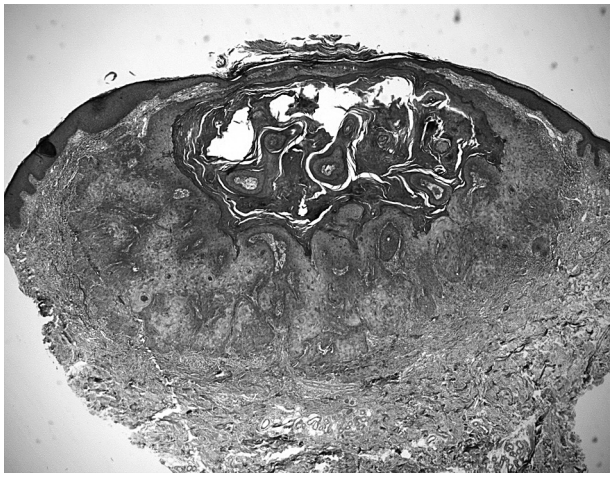

Fig. 1. Typical keratoacanthoma (KA) included in the present study. The keratoacanthoma is showing symmetry with two overhanging lips or shoulders and even a roof, with a central crater filled with keratin, and downgrowth of epithelial strands, partly with ground-glass appearance. In the dermis there is an inflammatory reaction.

One such marker could be HPV but no specific HPV type was predominating in our KA. If we had found such a HPV type, we certainly would have to determine its prevalence also in controls of SCC, in order to scientifically determine its association with KA. In an earlier study,[3] using the same nested polymerase chain reaction approach, the overall prevalence of HPV in SCCs, however, was similar to that of the KA in the present study [immunosuppressed patients; SCC, 71% (5/7) vs. KA, 55% (33/60)] [immunocompetent patients; SCC, 22% (2/9) vs. KA, 33% (4/12)].

The absence of a predominating HPV type in KA, and that there is no apparent difference in the HPV prevalence between KA and SCC is consistent with our conclusion that the role of HPV in the KA remains elusive.

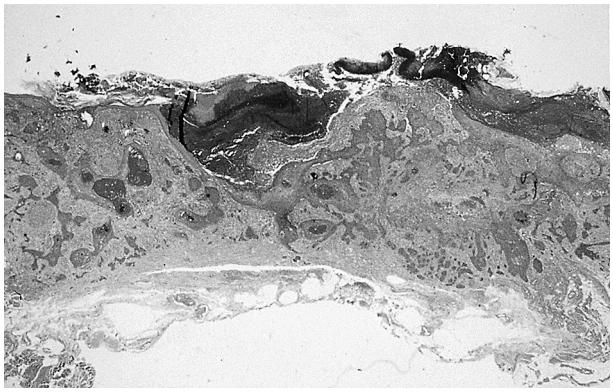

Fig. 2. A typical squamous cell carcinoma (SCC) with central ulceration and irregular downgrowth of infiltrating epithelial strands.

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