Keratoacanthomas and Spitz Tumors: Are They Both ‘Self-Limiting’ Variants of Malignant Cutaneous Neoplasms?

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From a purely morphological point of view, keratoacanthoma (KA) is a form of squamous cell carcinoma (SCC) since it reveals similar clinical and histopathological-cytological features as SCC [1]. However, it is well recognized that the morphological similarity between KA and SCC contrasts with their different biological attitudes. While SCC is a biologically malignant tumor characterized by the potential to progress, destroy tissue, metastasize and cause death, KA consistently undergoes spontaneous involution [1, 2]. For this reason, KA is widely accepted to be a self-limiting or ‘biologically benign’ variant of SCC.

Such a disparity between ‘malignant’ morphology and ‘benign’ biology exists also within the spectrum of melanocytic neoplasms, as in the case of Spitz tumors (ST). This group of melanocytic proliferations can be morphologically indistinguishable from melanoma but follow typically a benign clinical course [3–6]. Consequently, it is legitimate to question whether the concept of the existence of a ‘self-limiting’ variant can be extended to the spectrum of melanocytic ‘spitzoid’ tumors.

Indeed, common features between KA and ST do exist supporting such a concept, which we will discuss further in detail.

Evolution

The first striking similarity between KA and ST is represented by their evolution, which is characterized by 3 phases, namely growth, stabilization and involution, as shown in figure 1 [1, 7, 8]. The first phase is characterized by a rapid increase in size within a few weeks or months. Such a high proliferation rate is extremely unusual for any kind of benign melanocytic skin tumor and almost exclusively observed in biologically aggressive tumors such as nodular melanoma [9]. Thus, the growth attitude of KA and ST is in favor of the malignant nature of these cutaneous neoplasms.

In contrast, the subsequent stabilization and final involution deviate clearly from the expected course of a malignant tumor, and move KA and ST closer to the spectrum of benign skin neoplasms. Involvement of KA is a well-recognized phenomenon, but it has been only recently described in ST (fig. 2). In our original report, we observed the progressive disappearance of 2 cases of pigmented ST in children during a follow-up period of 6 months and 3 years, respectively [8]. Since then, further cases of involuting ST in children have been published [10–12]. Although these preliminary data do not allow estimating the proportion of ST undergoing involution,
they may plausibly explain the epidemiological figures of ST indicating a significant decrease in incidence after the 3rd decade of life [13].

‘Metastatic’ Potential

The second common phenomenon reported for KA and ST with malignant tumors is their potential to ‘metastasize’ to the regional lymph nodes [14, 15]. This ‘malignant’ attitude is particularly well documented for ST, for which the introduction of sentinel node biopsy as a diagnostic aid for histopathologically ambiguous tumors reopened the discussions whether these tumors are simply melanomas that were originally not recognized as such. Under the assumption that these tumors are unrecognized melanomas, one would expect the same morbidity and mortality rates of patients with lymph node metastases, independently from the diagnosis of the primary tumor. Interestingly, to date none of the patients with a primary diagnosis of ST and positive sentinel nodes in the published literature developed further metastases or died of metastases [15]. Similarly, cases of KA with perineural, vascular invasion or nodal involvement have been reported, but none died from progressive disease [14].

Genetics

Further intriguing data supporting that KA and ST can be seen as ‘biological siblings’ are coming from recent genetic studies. To summarize shortly the current status

Fig. 1. Clinical and digital dermoscopic follow-up showing the different evolutionary phases of a pigmented Spitz nevus located on the dorsum of the feet of an 8-year-old boy. A Baseline image at first presentation. Dermoscopy reveals brown to black globules. B Follow-up after 8 months reveals, besides a significant increase in size, a change of dermoscopic patterns from globular to prone reticular. C Follow-up 15 months after baseline presentation shows a progressive disappearance of pigmentation.
of research, H-ras mutations and copy number increase of chromosome 11p are associated with ST that reveal a pronounced cytological-histopathological atypia. Higher levels of cyclin D1 (i.e., a cell cycle promoter frequently found in melanomas) and increased expression of cell-cycle-inhibitory protein p16 are also found in ST exhibiting this chromosomal aberration [16–18]. H-ras is a member of the ras oncogenes (N-ras, K-ras) and its downstream target B-raf, which are thought to play an important role in melanocytic tumor development and proliferation. These genes serve as key signal transducers in the RAS/RAF/MAPK signaling pathway, which regulates diverse physiological processes including cell growth, differentiation and apoptosis [19]. While mutations in B-raf or N-ras are common in nevi and melanoma, H-ras mutations are seldom found in other than spitzoid melanocytic neoplasms [20]. Remarkably, oncogenic forms of H-ras, but not B-raf, induce a rapid cell-cycle arrest associated with a massive vacuolization and expansion of the endoplasmic reticulum in ST. This suggests that H-ras may play a direct role as gatekeeper in tumor control in ST [21].

Similarly to ST, mutations in H-ras are also substantially more frequent in KA than in SCC, although in KA this mutation occurs in association with a gain of chromosome 11q [22–24]. In addition, cyclin D1 overexpression is commonly observed in KA and SCC but is associated with functional p16 only in cases of KA, while in SCC there is a loss of p16 [25, 26].

These data have been obtained by independent studies focusing on either epithelial or melanocytic skin tumors. However, the models proposed to explain the tumorigen-
esis of KA and ST come basically to the same following conclusion: in the early phase of tumorigenesis, aberrations of chromosome 11 drive cell proliferation and altered cell differentiation via cyclin D1 overexpression, whereas p16 and possibly H-ras mutations seem to play a role in tumor growth control and probable final involution due to oncogene-induced senescence [21, 26].

Future studies comparing the genetic profile of KA and ST could shed more light onto the mechanisms involved in tumor growth, control and involution.

In conclusion, the attitude of growth, the metastatic potential and the genetics of KA and ST seem to be more than casually similar and support the concept that both tumors may be considered as self-limiting variants of their malignant counterparts.

Acknowledgment

Dr. Zalaudek is currently supported by the Elise Richter Program (V9-B05) of the Austrian Science Fund (FWF).

References


Dermatology 2009; 219: 3–6

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