

# When Is a Skin Cancer a Cancer: The Histopathologist's View

# 2

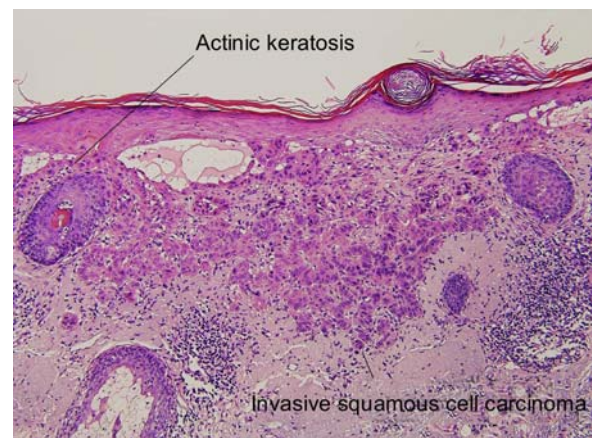
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## Key Points

- › In the initial phase of field cancerization, a patch of abnormal cells arises from a genetically altered stem cell.
- › With molecular techniques, precancerous clonal fields that are 7 cm and greater in diameter have been detected in oral and esophageal mucosae. No data exist regarding the skin.
- › Individual cells in an AK may be every bit as atypical as those in an invasive SCC.
- › A specimen that provides adequate depth is key to a correct diagnosis.
- › Once a tumor has invaded, there is little consensus as to what histologic features should be cited in the pathology report.
- › In SCC carcinoma type, Breslow thickness, level of invasion, ulceration, growth pattern, and mitotic index may be relevant histological features.
- › Molecular techniques may aid the histopathological diagnosis.

## 2.1 Field Cancerization from the Dermatopathologist's Point of View

Non-melanoma skin cancers typically develop on a background of “sun damage” characterized by solar elastosis as well as varying degrees of epithelial atypia and architectural disorder. Molecular data from both skin and other organs suggest that these observations are manifestations of field cancerization. The presence of widespread actinic keratoses (AKs) and the high incidence of multiple primary cutaneous cancers in patients with severe sun damage are the most obvious manifestations of field cancerization in the skin. The finding of cutaneous squamous cell carcinomas (SCCs) arising within actinic keratoses (Fig. 2.1) is evidence of multi-stage carcinogenesis where progressive genetic aberrations eventually result in an invasive cancer arising on a background of field cancerization. This chapter examines the concept of field cancerization from the dermatopathologist's point of view as well as histologic and



**Fig. 2.1** Invasive SCC arising in an actinic keratosis

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**Table 2.1** Histologic and molecular evidence supporting field cancerization in NMSC

SCCs commonly arise in AKs
AKs demonstrate a spectrum of cytologic changes similar to SCC
Cytologic features of the actinic keratosis typically resemble those of the invasive component
Shared molecular aberrations that impart a growth advantage to both cell populations, including p53 mutations and phosphorylation, upregulation of cyclooxygenase (COX)-2 expression, and E-cadherin gene promoter hypermethylation
Multiple p53 mutations in adjacent normal-appearing skin
Cytogenetic evidence that multiple primary tumors represent distinct clones arising on a background of atypical cells

molecular methods to determine when a proliferation of atypical cells crosses the threshold to a malignancy competent to produce metastatic disease (Table 2.1).

The concept of field cancerization was first proposed by Slaughter in 1953 to explain the histological alterations in the mucosa surrounding oral squamous cell carcinoma. The concept has evolved to encompass a spectrum of multifocal neoplastic or preneoplastic changes. Field cancerization has been described in a variety of tissues that include the oral mucosa, esophagus, stomach, colon, anal mucosa, cervix, bladder, and skin.

In the initial phase of field cancerization, a patch of abnormal cells arises from a genetically altered stem cell. Mutations such as p53 that impart a growth advantage allow the patch to create an expanding precancerous field. With molecular techniques, precancerous clonal fields that are 7 cm and greater in diameter have been detected in oral and esophageal mucosae [1]. Ultimately, additional mutations lead to clonal divergence and the development of cancers within the precancerous field. Field cancerization helps explain the presence of multifocal tumors and the formation of new tumors in an area where one cancer has been resected. Multiple p53 mutations can be detected by DNA sequence analysis in normal-appearing skin adjacent to non-melanoma skin cancer of the head and neck [2]. Cytogenetic analyses of basal cell carcinomas have indicated that some tumors are composed of multiple cytogenetically unrelated clones, suggesting that field cancerization can result in clinically inapparent “collision tumors” [3]. Psoralen and ultraviolet A (PUVA) therapy may increase risk of non-melanoma skin cancer through p53 and other mutations that lead to field

cancerization. Signature PUVA-induced mutations differ from those produced by ultraviolet light alone [4].

The presence of field cancerization has been used to explain the high incidence of second tumors in patients with head and neck cancer. In one study, 21 patients with head and neck cancer, infusions of iododeoxyuridine and/or bromodeoxyuridine followed by monoclonal antibody staining identified epithelial disorder with suprabasal S-phase nuclei in tissue surrounding the cancer, supporting field cancerization [5]. Clonal expansion has been demonstrated in tissue surrounding gastric carcinomas by identification of mitochondrial DNA mutations through laser-capture microdissection and polymerase chain reaction [6]. Selective growth advantage of clones of normal-appearing cells surrounding both colon and head and neck cancers is imparted by TGFBR1\*6A, a variant of the type I transforming growth factor (TGF)-beta receptor (TGFBR1). The highest ratio of abnormal to normal allele is present at the tumor edge, but extends at least 2 cm from the tumor [7]. 14-3-3 sigma, a cell cycle regulating protein, is often lost in cancers as a result of hypermethylation or induction of a ligase that targets the protein for proteasomal degradation. Loss is also noted in the surrounding apparently normal tissue, suggesting a role in field cancerization. The normal protein acts as a tumor suppressor through binding to eukaryotic initiation factor 4B. In the absence of the protein, aberrant mitotic translation often results in binucleate cells or aneuploidy [8]. About 72% of the mucosal biopsies adjacent to squamous cell carcinoma of the head and neck demonstrate aberrations in protein expression similar to the adjacent cancers [9]. Methylation of O-6-methylguanine-DNA methyltransferase (a DNA repair gene) is frequently found in colorectal cancer as well as the apparently normal adjacent mucosa [10]. In patients with lung cancer, evidence of allelic imbalance and alterations in p53 and cyclin D1 expression are found in 83% of specimens from histologically normal areas of the bronchi of the upper and lower lobes [11].

Telomeres stabilize the chromosome. When telomere shortening reaches a critical threshold, chromosomal instability results in “genomic crisis” with widespread cell death and the potential for immortal clones. Telomere measurement via quantitative fluorescence in situ hybridization has identified telomere shortening in esophageal squamous cell carcinomas, but also in nearby non-neoplastic esophageal epithelium [12]. Evidence of altered telomeres as well as unbalanced allelic loci are

present in breast tumors and adjacent normal-appearing tissue extending at least 1 cm beyond the tumor [13].

The evidence supporting field cancerization in the skin and other organ systems is overwhelming. It explains the presence of fields of AKs in sun-damaged skin and the eventual progression to invasive SCC. It remains for the dermatopathologist to determine when that transition takes place.

## 2.2 Histologic Diagnosis of Skin Cancers

Clinical misdiagnosis of SCC as “hypertrophic AK” is particularly common on the dorsal hands, ears, and scalp. Various new technologies, including dermoscopy, spectroscopy, confocal microscopy, ultrasonography, computed tomography, magnetic resonance imaging, optical coherence tomography, fluorescence imaging, positron emission tomography, and terahertz imaging have been investigated as means of noninvasive tests to improve clinical diagnosis of possible skin cancers, but to date none has replaced biopsy as the gold standard [14].

Both AK and SCC can demonstrate a spectrum of cytologic changes from mild to high-grade atypia. Features of high-grade atypia include a high nuclear to cytoplasmic ratio, nuclear hyperchromasia, prominent nucleoli, red nucleoli, nucleoli with stems, and the presence of a thick irregular nuclear envelope. Individual cells in an AK may be every bit as atypical as those in an invasive SCC, and karyometric analysis has not been successful in distinguishing the two [15]. Actinic keratoses with high-grade atypia are likely to give rise to invasive SCC, and the cytologic features of the actinic keratosis typically resemble those of the invasive component.

I will not dwell on the debate regarding nomenclature for actinic keratoses. Suffice it to say that some believe that all actinic keratoses should be termed keratinocytic intraepithelial neoplasia (KIN) or SCC in situ. Others feel that these designations are not an improvement over the term actinic keratosis and do little to improve the care of patients. Regardless of what terms we use, the molecular data cited above suggest that tumorigenesis in skin is a multistep process in which clones of cells gain a growth advantage that allows them to expand over large areas of skin. Successive

aberrations eventually lead to competence for invasion and metastasis. The focus of my discussion will be on how the pathologist determines when a population of atypical squamous cells gains competence to invade and metastasize.

An adequate specimen is critical for the accurate diagnosis of non-melanoma skin cancers. In a study of 57 consecutive patients with penile squamous cell carcinoma, the interpretation of the initial biopsy was discordant with staging at the time of penectomy in 30% of cases. In two patients, a diagnosis of cancer could not be established in the initial biopsy material. The depth of invasion could not be determined in 91% of the biopsy specimens [16]. In contrast, a retrospective study of 40 consecutive periocular tumors found the biopsy results to be concordant with the excisional specimen in 19 of 20 incisional biopsy specimens and 17 of 20 punch biopsy specimens [17]. A specimen that provides adequate depth is key to a correct diagnosis.

Histologic invasion is characterized by irregular islands of cells or single keratinocytes that breach the basement membrane zone and extend between collagen bundles into the zone of solar elastosis. Hyperplastic AKs demonstrate a complex pattern of budding that extends into an expanded papillary dermis, but not the reticular dermis or the zone of solar elastosis. Step sections may be required to demonstrate the area of invasive carcinoma.

Once a tumor has invaded, there is little consensus as to what histologic features should be cited in the pathology report. Synoptic reporting modules for non-melanoma skin cancer exist, just as they do for melanoma, but they are seldom used [18]. A study of 184 patients with cutaneous squamous cell carcinoma evaluated carcinoma type, Breslow thickness, level of invasion, ulceration, growth pattern, and mitotic index as risk factors for recurrence or metastasis. Ulceration was a significant risk factor for metastasis, as were level and thickness. Mitotic index and degree of differentiation were somewhat important [19]. Cassarino, Derienzo, and Barr separate cutaneous squamous cell carcinomas into categories with a low ( $\leq$  or  $= 2\%$ ), intermediate (3–10%), or high ( $>10\%$ ) risk of metastasis. Low-risk SCCs include those tumors arising in actinic keratosis, HPV-associated tumors, trichilemmal carcinoma, and SCCs unassociated with radiation. The intermediate-risk category includes acantholytic SCC, intraepidermal epithelioma with invasive carcinoma, and lymphoepithelioma-like carcinoma. The high-risk types include those in immunosuppressed

patients, anaplastic invasive carcinoma originating in Bowen’s disease, de novo SCC, adenosquamous carcinoma, malignant proliferating pilar tumors, and SCC arising in radiation ports and burn scars [20, 21].

2.3 Advanced Diagnostic Techniques

The number of silver-stained nucleolar organizer regions (AgNORs) becomes progressively higher with tumor progression from AK to SCC ( $P < 0.001$ ) [22]. Interpretation requires experience and pathologists must be careful that they are counting AgNORs rather than nucleoli.

A study of nuclear Ki-67 (MIB-1) expression 15 actinic keratoses and seven invasive squamous cell carcinomas showed staining of basal and suprabasal nuclei in actinic keratoses to the mid-zone of the epidermis. In invasive squamous cell carcinomas, MIB-1 positivity was variable in all layers of the epidermis [23]. In a study of expression of markers associated with tumor progression, p53 was moderately expressed in AKs and strongly expressed in SCCs, p63 staining was variable in SCC, but strong in AK, survivin was confined to the basal layer in AKs but more diffusely expressed in eight of ten SCCs, and and hTERT was strongly expressed in both [24]. In another study, immunoperoxidase staining for p53 and bcl-2 protein expression was greater in invasive SCC than in AK [25] (Table 2.2). Oh et al. found that nuclear expression of p27 is decreased in invasive squamous cell carcinoma. Ki-67 expression is increased and is more likely to be seen in tumor islands while it is restricted to the basal layer in AKs [26].

Fas ligand expression increases in both T cells and epithelial cells with progression from AK to SCC. In one study, FasL-expressing tumor cells were present in nine of 18 SCCs, compared with only one of 20 AKs ( $P < 0.005$ ) [27].

**Table 2.2** Histologic features that distinguish invasive SCC from AK

Irregular islands
Single-file keratinocytes
Cells breach the basement membrane zone
Cells extend between collagen bundles
Cells extend into the zone of solar elastosis

A study of cyclin A and beta-catenin expression by immunohistochemistry in actinic keratoses and invasive SCC found that diffuse cyclin A expression was more common in poorly differentiated tumors ( $P < 0.0001$ ) and reduced or absent membranous beta-catenin staining was found more often in SCC than in AK ( $P = 0.03$ ) [28]. A study of protein and mRNA expression of RPE65 in actinic keratosis and squamous cell carcinoma found that mRNA expression was reduced in both. Protein expression was reduced and quite irregular in AK and absent in invasive SCC [29].

Some authors have found that the intensity of p16 protein expression is greater in SCC than in AK and progression from actinic keratosis to SCC of the skin is correlated with deletion of the 9p21 region encoding p16 [30–32]. Aberrant expression of nuclear lamins A and C is noted in skin tumors, and the staining with lamin C tends to be more diffuse in SCC than in AK [33]. Expression of the retinoblastoma protein p16 INK4a is weak in AK, and stronger in invasive SCC with strongest staining toward the center of the tumor [34]. Metalloproteinase-2 expression is predictive of the aggressiveness of cutaneous SCCs [35]. Staining intensity correlates with cellular atypia, neovascularization, inflammation, and the invasive tumor front.

Other molecular techniques have shown little value in distinguishing SCCs from AKs. In an immunohistochemical study of p53 phosphorylation state in 44 AKs and 62 SCCs, overexpression was similar in both, suggesting it is an early change in the pathogenesis of SCC and has little value in differentiating AK from SCC [36] (Table 2.3). Similarly, analysis of promoter hypermethylation of death-associated protein kinase

**Table 2.3** Promising advanced diagnostic tests to distinguishing invasive SCC from AK

AgNOR counts
p63 expression
Survivin expression
p53 expression
bcl-2 protein expression
p27 expression
Ki-67 expression
Fas ligand expression
Cyclin A expression
Beta-catenin expression
RPE65 expression
p16 expression
Lamin expression
Metalloproteinase expression



**Table 2.4** Advanced diagnostic tests that do not appear to distinguish invasive SCC from AK

p53 phosphorylation state
Promoter hypermethylation of death-associated protein kinase
Promoter hypermethylation of p16 tumor suppressor gene (COX)-2 expression
E-cadherin gene promoter hypermethylation
Expression of endothelin

and p16 tumor suppressor gene were each found in one of seven SCCs and none of nine AKs, making it unlikely that these markers will be helpful in distinguishing the two. Cyclooxygenase (COX)-2 expression is upregulated in both AKs (31%), and SCC (40%) [37]. E-cadherin gene promoter hypermethylation was detected in six of seven cases of invasive squamous cell carcinoma, and four of nine AKs [38]. A study using quantitative polymerase chain reaction to measure the level of gene transcription of three endothelin proteins and two endothelin receptors found no significant increase in expression in AK, Bowen's disease, or SCC, suggesting these assays are of little value in predicting tumor progression for cutaneous squamous cancers [39] (Table 2.4).

While molecular techniques have improved our ability to distinguish SCCs from AKs, they have also reinforced the concept that non-melanoma skin cancers arise through a complex series of aberrations at the molecular level. Actinic keratoses represent a spectrum along the continuum to invasive cancer. They are the most visible manifestation of field cancerization which creates a population of atypical cells with the potential to progress to invasive malignancy capable of metastasis.

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