

Squamous Cell Carcinoma

A Review of Etiology, Pathogenesis, Treatment, and Variants

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ABSTRACT: There are a multitude of malignant neoplasms that can, with the right genetic predisposition and exposure, affect the human body. The most common of these malignancies are the nonmelanoma skin cancers. There are two main forms of nonmelanoma skin cancer, basal cell carcinoma and squamous cell carcinoma. Of the two, squamous cell carcinoma is the second most prevalent but is potentially more devastating and life-threatening form of nonmelanoma skin cancer. This article describes the incidence, genetics, and etiology of squamous cell carcinoma. Also, this article defines squamous cell carcinoma stages of progression from precancerous to malignant and the various treatment modalities that are used in each stage of development. Finally, this article discusses the various forms of squamous cell carcinoma and the physiological changes that occur within the skin because of this malignancy.

Key words: Squamous Cell Carcinoma, Pathogenesis, Treatment

There are a multitude of malignant neoplasms that can, with the right genetic predisposition and exposure, affect the human body. The most common of these malignancies are the nonmelanoma skin cancers. There are two main forms of nonmelanoma skin cancer, basal cell carcinoma and squamous cell carcinoma. Of the two, squamous cell carcinoma is the second most prevalent, but it is potentially more devastating and life threatening.

OBJECTIVES

The following are the objectives of the study:

1. Describe the prevalence, genetics, and etiology of squamous cell carcinoma.

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2. Define the stages of progression of squamous cell carcinoma from precancerous to malignant and the various treatment modalities that are used in each stage of development.
3. Discuss the various forms of squamous cell carcinoma and the changes that occur within the skin because of this malignancy.

BACKGROUND

The prevalence of cutaneous squamous cell carcinoma in lightly pigmented individuals is 58.25 per 100,000, and for darker pigmented skin colors, it is 3.09 per 100,000. The head and neck region is the most commonly affected, comprising 67% of the cases. Although rare, squamous cell carcinoma is the most common form of cutaneous malignancy among darker pigmented populations. The mortality rates are low for squamous cell carcinoma, but they are higher in men and increase with age. For lightly pigmented men, the mortality rate is 0.38 per 100,000, and for lightly pigmented women, the rate is 0.23 per 100,000. The most common primary site that contributes to mortality is the ear (Miller & Moresi, 2003).

ETIOLOGY AND PATHOGENESIS

The exact genetic alterations and numbers of mutations needed for malignant transformation are as yet unknown. The most readily accepted theory involves the transformation of the epidermal p53 gene clones by ultraviolet (UV) exposure to the precursors of squamous cell carcinoma. Early p53 mutations are believed to inhibit apoptosis of abnormal cells, allowing them to expand at the expense of normal presenting cells. Alterations of the p53 gene are the most common presenting malformation in all stages of squamous cell carcinoma, starting at the precancerous lesion and advancing to the invasive and potentially metastatic forms. Typically, this presents with one allele (DNA sequence) containing a missense point mutation with a UV signature, and the remaining allele is deleted (Ponten & Lundeberg, 2003).

The pathogenesis of squamous cell carcinoma is multifactorial and includes many extrinsic and intrinsic factors.

The most important extrinsic factor is generally recognized as UV sunlight exposure. As lifetime UV exposure increases, so does the incidence of squamous cell carcinoma (Marks, 1996). In fact, for every 8- to 10-degree decrease in latitude (e.g., Washington, DC to Tampa, FL), there is a doubling of the incidence of squamous cell carcinoma. Patients treated with psoralen with ultraviolet A are 30 times more likely to develop squamous cell carcinoma than the general population (Lohmann & Solomon, 2001). The human papillomavirus type 16 is present in many of the genital and periungual forms of squamous cell, but human papillomavirus types 5, 8, 9, 18, 31, 33, 35, 39, 40, and 51–60, have all been isolated from squamous cell tumors (Wolff, Johnson, & Suurmond, 2005). Other extrinsic factors that are related to the development of squamous cell carcinoma are industrial carcinogens, such as pitch, tar, crude paraffin oil, fuel oil, creosote, lubricating oils, arsenic, and nitrosoureas (Wolff et al., 2005).

Intrinsic factors associated with squamous cell carcinoma include age, lighter skin pigmentation, scars, and dermatoses associated with photosensitivity (chronic cutaneous lupus), ulcerations, and lichen planus (Lohmann & Solomon, 2001). There are two hereditary conditions that increase the risk of developing squamous cell carcinoma. Xeroderma pigmentosa is an autosomal recessive condition leading to an inability to repair UV-induced DNA damage. Oculocutaneous albinism results in insufficient melanin production, thereby decreasing the body's defense against UV damage (Miller & Moresi, 2003). Immunosuppressed individuals, whether by AIDS or organ transplant, have shown not only an increased incidence of squamous cell carcinoma but also a tendency to develop more aggressive tumors (Lohmann & Solomon, 2001).

SQUAMOUS CELL CARCINOMA: DEVELOPMENT, VARIANTS, AND TREATMENT

The prototypical invasive squamous cell lesion can be identified with relative ease by its appearance. Most commonly, they are indurated papules, plaques, or nodules, with thick adherent scale or hyperkeratosis (Wolff et al., 2005). Fortunately, many squamous cell carcinomas move through multiple stages before reaching the invasive presentation. If these precursors are identified, more conservative treatments can be utilized.

Actinic Keratosis

The actinic keratosis is the first observable precursor to an invasive squamous cell carcinoma (Figure 1). Histologically, an actinic keratosis is defined by atypical keratinocytes, arising in the stratum spinosum, which extend up to but do not involve the stratum corneum (Figure 2). These keratinocytes are enlarged and crowded and show loss of polarity (Miller & Moresi, 2003). Clinically, aci-

tic keratoses present as less than 1 cm, tan-brown, red, or skin-colored, rough, sandpaper-like patches (Figure 2). Cutaneous horns can develop in lesions that produce excess keratin (Murphy, Sellheyer & Mihm, 2005). The most common sites of occurrence are the face, ears, and dorsum of the hands and arms (Wolff et al., 2005). These precancerous lesions can be treated conservatively and successfully with cryosurgery, electrodesiccation and curettage, chemotherapeutic creams, or topical immune modulators (Chang, Madkan, Cook-Norris, Sra, & Tying, 2005; Marks, 1996). Without treatment, it is generally believed that a percentage of these lesions will spontaneously resolve, but some can continue to mutate and form squamous cell carcinoma in situ.

Squamous Cell Carcinoma In Situ

Clinically, squamous cell carcinoma in situ presents as a well-demarcated, scaling, or hyperkeratotic macule, papule, or plaque (Figure 3). They can be nearly indistinguishable from actinic keratoses to the naked eye. Evidence of erosion and, at times, evidence of bleeding should increase clinical suspicion (Wolff et al., 2005). Histopathologically, squamous cell carcinoma in situ involves the entire thickness of the epidermis with pleomorphic (multiple sizes and shapes) keratinocytes, and involves the adnexal epithelium (Figure 4). No evidence of invasion into the dermis is observed (Miller & Moresi, 2003). Like their precursors, squamous cell carcinoma in situ may be treated with cryosurgery, electrodesiccation and curettage, chemotherapeutic creams, excision, and topical immune modulators (Chang et al., 2005; Marks, 1996). Without timely and appropriate treatment, these lesions can advance to form invasive squamous cell carcinoma.

Invasive Squamous Cell Carcinoma

The common invasive squamous cell carcinoma (Figure 5) is a malignancy of the keratinocytes from the epidermis that invade the dermis. Having transversed the basement membrane, these malignancies have the potential to



FIGURE 1. Actinic keratoses on dorsal hands.

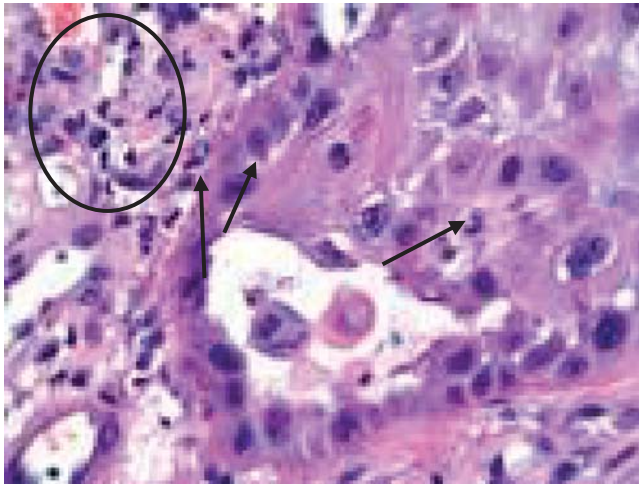


FIGURE 2. Actinic keratosis. Note the irregular nuclei of varying size.

invade fat, muscle, bone, and cartilage and to metastasize to regional lymph nodes and distant sites (Miller & Moresi, 2003). The cells of an invasive squamous cell carcinoma resemble those of an actinic keratosis. They have enlarged and irregularly contoured nuclei, increased numbers of nucleoli, and irregular mitotic figures (Figure 6). The important clinical distinction is that there is invasion into the dermis, which necessitates more aggressive treatment to prevent further damage to the surrounding cutaneous and underlying structures, and metastasis. Surgical excision is the treatment of choice for all invasive tumors. Usually, treatment is performed under local anesthesia with a 3- to 4-mm margin taken. For high-risk lesions, such as those on the face, ears, and lips, as well as recurrent tumors and tumors larger than 2 cm, Mohs micrographic surgery should be employed to ensure the



FIGURE 3. Squamous cell carcinoma in situ on medial aspect of upper calf.

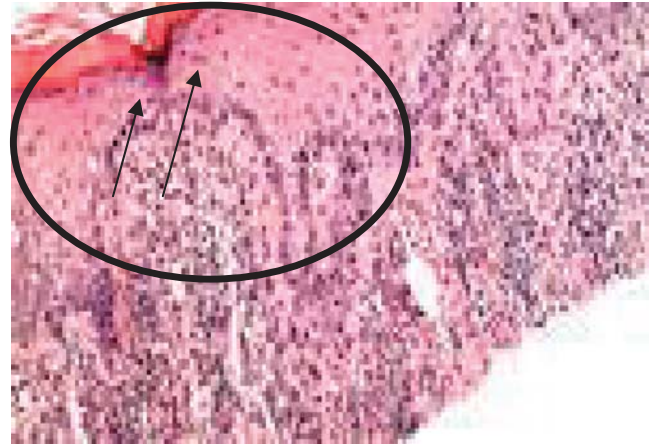


FIGURE 4. Squamous cell carcinoma in situ showing atypical keratinocytes approaching the stratum lucidum.

highest possible cure rate (Marks, 1996). Failure to treat or insufficient treatment can lead to recurrence and metastasis.

There are many factors that contribute to the aggressiveness, recurrence rate, and metastatic potential of squamous cell carcinomas. Tumor size is a major determinant. For lesions larger than 2 cm, the recurrence rate doubles and the metastatic rate triples to 30%. Tumors with rapid growth rates also have a higher metastatic potential. Tumors originating in burn scars have a 30% metastasis rate. The rate for metastatic disease increases the closer a tumor is to the oral cavity. Recurrent tumors also have a greater metastatic rate, especially on the lips and ears, where the rate is 32% and 45%, respectively (Lohmann & Solomon, 2001). Metastasis from squamous cell carcinoma appears most commonly in the regional lymph nodes, followed by the lungs and liver (Marks, 1996).

Squamous cell carcinoma would be relatively easy to diagnose and treat if the common variety were all that



FIGURE 5. Invasive squamous cell carcinoma on the scalp.

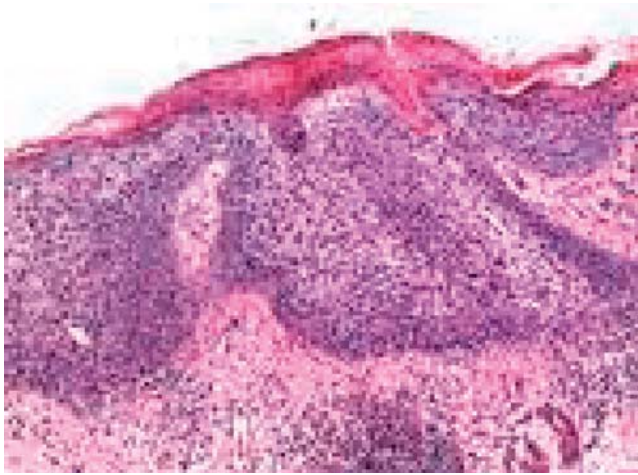


FIGURE 6. Full thickness atypia, extending into the dermis (dermis is not shown).

existed. There are, however, multiple variants of this disease, including spindle cell, acantholytic, verrucous, lymphoepithelioma-like, desmoplastic, adenosquamous, cystic, and keratoacanthoma (Miller & Moresi, 2003). Each of these variants differs in histology and prognosis, but the treatment is identical to the more common form.

Spindle cell carcinoma is a rare variant in which the neoplastic keratinocytes infiltrate the dermis as single cells with elongated nuclei (Miller & Moresi, 2003). Associations with previous trauma or radiation have



FIGURE 7. Verrucous squamous cell carcinoma on the lower leg.

been reported. These tumors are most often found on the face or other sun-exposed regions of older persons. Due to a lack of keratinization, these lesions are difficult to detect and diagnose (Lohmann & Solomon, 2001). In addition, because differentiation is minimal in these lesions, recurrence and metastatic rates are high (Miller & Moresi, 2003).

Acantholytic squamous cell carcinoma is identified histologically by the cells being arranged in cords and nests, with clefts produced by acantholysis of cells leaving spaces resembling glands. These lesions usually present as ulcerations or nodules on the head and neck of men in their fifth to sixth decades (Lohmann & Solomon, 2001). It is believed that this variant is more aggressive and poses a greater risk of metastasis (Miller & Moresi, 2003).

Verrucous squamous cell carcinoma is a low-grade variant that is typified by well-differentiated keratinocytes lacking significant atypia (Miller & Moresi, 2003; Figure 7). These are not believed to have a metastatic risk and are identified by their location. The three main forms are oral, plantar, and Buschke-Loewenstein tumors (Lohmann & Solomon, 2001).

Lymphoepithelioma-like carcinoma is a rare form of squamous cell carcinoma, recently classified by the World Health Organization. Its histogenesis is as yet uncertain. Due to the presence of sebaceous, eccrine, and trichilemmal differentiation within these neoplasms, it is widely believed that they originate in adnexal structures. These tumors have also been identified in the nasopharynx, salivary glands, thymus, lung, stomach, uterine cervix, and vagina. Therefore, when lesions are found on the skin, metastasis from another primary site must be considered. These tumors are composed of infiltrating cords and islands of pale epithelial cells that lack epidermal or adnexal connections (Miller & Moresi, 2003).



FIGURE 8. Keratoacanthoma. Note the crateriform morphology.



FIGURE 9. Keratoacanthoma on the lower leg.

Desmoplastic squamous cell carcinomas are another subtype that has an increased risk of recurrence and metastasis. The most common site for these tumors is the ear. Histologically, these tumors are characterized by infiltrating cords of neoplastic keratinocytes with a dense sclerotic stroma that comprises at least one third of the tumor. Perineural invasion and cytological atypia are often present (Miller & Moresi, 2003).

Adenosquamous carcinoma is a form of squamous cell carcinoma that has the cytological features of both a keratinocyte-derived epidermal tumor and a gland-derived epithelial tumor. Its architecture is identical to the common squamous cell carcinoma except for the presence of deeply invasive nests and gland-like cystic spaces with areas of mucin production (Miller & Moresi, 2003).

Cystic squamous cell carcinoma is a variant that typically occurs in older persons on the lower extremities and the dorsal aspects of the hands. This histological subtype closely resembles the common squamous cell carcinoma with the addition of large, intradermal keratin-filled cysts. Superficial sampling of these tumors may result in the misdiagnosis of an epidermoid cyst (Miller & Moresi, 2003).

Keratoacanthomas are a distinct and interesting subtype of squamous cell carcinoma. The debate still rages as to whether this is a form of squamous cell and if it should be treated as a malignancy at all. Histologically, these tumors resemble the common squamous cell carcinoma and at the early stages are nearly indistinguishable (Figure 8). In the mature tumor, there is a crateriform squamous proliferation with a central core of compact hyperkeratosis

(Figure 9). These tumors evolve rapidly over weeks to months, and then many will spontaneously resolve. There are many factors associated with the development of these lesions, including solar radiation, trauma, genetics, and possible viral etiologies (Sarabi, Selim, & Khachemoune, 2007). There are various forms of keratoacanthomas including Grzybowski, Ferguson-Smith, and Witten and Zak (Wee, 2004).

CONCLUSIONS

In conclusion, this article has discussed the etiology, stages of development, treatment, and multiple forms of squamous cell carcinoma. This is a diverse disease with many cytological and clinical variants. It is important to note that, as with all cancers, early diagnosis and treatment is the key to survival. The advantage of skin cancer is that we can see the tumor as it develops; one only has to look and be equipped to recognize the changes it manifests in the skin.

NURSING IMPLICATIONS

It is imperative that dermatology nurses and advanced practice dermatology nurses understand the developmental aspects of the diseases that face them everyday in practice. Knowing the etiology, pathogenesis, treatment options, and variants of squamous cell carcinoma can improve the rate of diagnosis and the selection of treatment options, patient outcomes, and ongoing patient education and care. ■

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