Pigmented Squamous Cell Carcinoma of the Oral Mucosa
—With Special Reference to the Role of Non-keratinocytes in Tumors and Tumorous Conditions—

by

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Introduction

Stratified squamous epithelium is a mixed cell population made up of two cell types each having different functions; keratinocytes and non-keratinocytes. The latter, also referred to as dendritic clear cells or interepithelial cells, is divided mainly into melanocytes, Langerhans cells and Merkel cells[1-5]. The interactions between keratinocytes and non-keratinocytes in normal conditions were reviewed by PRUNIERAS[2] in 1969. However, the role of non-keratinocytes in pathologic conditions is not fully recognized[3].

In the WHO publication Histological Typing of Oral and Oropharyngeal Tumours, squamous cell carcinoma is defined as a tumor consisting of irregular nests, columns or strands of malignant epithelial cells, infiltrating subepithelially, and tumor cells may resemble any or all of the layers of stratified squamous epithelium [6,7]. Common histological variants such as verrucous carcinoma, spindle-cell carcinoma, adenoid squamous cell carcinoma and lymphoepithelioma are categorized in the WHO classification[6,8]. One rare variant, pigmented squamous cell carcinoma, is of particular importance since it may be confused with a variety of pigmented lesions. This unusual variant is characterized histologically by the presence of numerous pigment blockade melanocytes within the tumor. Several cases have been described in the skin[9-11], the cornea and conjunctiva[12-14].

PATAKAS et al.[15] in 1974 reported the first case of oral pigmented squamous cell carcinoma in which they described a tongue tumor in a 47-year-old Negro male. To our knowledge, there are no subsequent reports in the literature. In this paper we report on a typical case having a rare variant of the tongue and also three cases of oral squamous cell carcinoma containing pigment blockade melanocytes within the tumor nests. The purpose of this study is to discuss the role of non-keratinocytes in several pathologic conditions.

Case Report

The histopathologic slides from 400 consecutive lesions coded as squamous cell carcinoma of the oral mucosa on file at our laboratory from 1966 to 1980 were reviewed. Only one case (Case 1) presents a clinically and histologically identical
Three cases (Cases 2, 3 and 4) show the presence of pigment blockade melanocytes within the tumor microscopically. In all cases, only a single hematoxylin and eosin slide was available for study.

Case 1

In May 1973, a 47-year-old male was admitted to the Nihon University Dental Hospital. One year previously he had noticed a slow-growing tumor on the left lateral border of his tongue that had increased rapidly in size during the last few months. This sessile dome-shaped tumor with ulcer was about 3 cm at its greatest diameter. At the surface of the tumor spotty pigmented areas were noted. This pigmentation was dark brown in color and was considered to be melanin. All further
laboratory investigations were normal.

**Histology** The biopsy specimen included normal mucosa with the underlying stroma and muscle. The tumor was composed of atypical squamous cells showing marked pleomorphism and a disorderly pattern. Numerous abnormal mitosis and keratin pearls were seen in the tumor nests. The tumor cells deeply invaded the muscular tissue. The pigment blockade melanocytes were interdispersed among the tumor cells and were more prominent in the areas of intraepithelial lateral invasion than in the deeply invasive areas. The dendritic shapes of the melanocytes were clearly demonstrated by their abundant contents of melanin granules (Figs. 1 and 2). The stroma around these nets showed numerous melanophores and severe chronic
inflammatory cell infiltration. No hyperpigmentation of melanin was noted in the normal adjacent epithelium.

**Case 2**

A 30-year-old male was seen in the Nihon University Dental Hospital (February 1969) with a tongue tumor of about 2 cm in diameter. It was located at the right border of the tongue. The overlying mucosa showed no pigmentation. No other relevant clinical abnormalities were found.

**Case 3**

In January 1966, a 59-year-old male was seen in the Nihon University Dental Hospital. He had an ulcerated, painless tumor of about 4 cm in diameter localized at the lingual surface of the left mandibular gingiva. It had been present for one year. No pigmentation became obvious. Other clinical abnormalities were not found.

**Case 4**

A 44-year-old female was admitted to the Nihon University Dental Hospital in November 1972. A slow-growing ulcerated tumor with a diameter of 2 cm had developed on her right mandibular gingiva during the previous one year. There were no pigmented areas in this tumor. Further clinical investigations were normal.

**Histology.** Cases 2, 3 and 4 all showed a similar histology. The biopsy specimens were composed of atypical squamous cells displaying marked pleomorphism. The tumor cells were arranged in disorderly pattern and showed abnormal mitosis. Numerous keratin pearls were found. The deeply infiltrating tumor nests contained a few pigment blockade melanocytes as compared with that of Case 1 (Figs. 3 and 4). Also there were no melanophores in the stroma and no pigmentation in the adjacent normal epithelium.

**Discussion**

Oral epithelium as well as skin epithelium is made up predominantly of keratinocytes, which comprise over 80-90% of the cells present. Non-keratinocytes make up about 10-15% of the cells in the epithelium, with Langerhans cells constituting about 10%, melanocytes about 3-5% and rarely occurring Merkel cells[4]. Other non-specific cells such as lymphocytes and cerebriform cells (Sezary-like cells), lacking specific ultrastructural features, are also recognized[16-19]. All these cells appear in routine paraffin-embedded histologic sections as “clear cells”.

Melanocytes synthesize melanin pigment in the form of small organelles called melanosomes and transfer them to the adjacent keratinocytes by a dendritic process that has been called “inoculation”. These cells may be identified as pigment blockade melanocytes in routine hematoxylin and eosin sections by their abundant content of melanin granules under several pathologic conditions.

Although Lund & Kraus[20] reported that 7% of squamous cell carcinoma of the skin are pigmented, most authors postulated that melanin pigmentation is extremely rare[9,11]. Squamous cell carcinoma that rarely allows the symbiosis of melanocytes is of a special type; intermediary (metatypical) type or poorly keratinizing (Bowenoid) type. This type of cancer is characterized histologically by the proliferation of neoplastic keratinocytes resembling basal cells[8,9,11]. It is known that basal cell carcinoma of the skin often shows melanin pigmentation[8], and
this pigmented variant is the most common type in Japan[11].

Reported cases of oral pigmented squamous cell carcinoma including our present case (Case 1) are found to occur in the tongue. A case of PATAKAS et al.[15] diagnosed as “squamous cell carcinoma in situ” is considered to be Bowen's disease of the oral mucosa (Bowenoid lesion). Our present case shows a typical feature of well-differentiated squamous cell carcinoma where the pigment blockade melanocytes are mostly found in the areas of intraepithelial lateral invasion rather than in the areas of stromal invasion. Similar observations have been described in skin tumors [9]. In the human tongue melanin pigmentation is rare[21,22] and also pigmented lesions are extremely rare[23–25]. However, SATO[26] reported that the pigment blockade melanocytes are usually found in the human tongue epithelium, and suggested that this is a characteristic feature compared to that of skin epithelium. We consider from these observations that pigment blockade melanocytes in squamous cell carcinoma may be reactive to and stimulated by the presence of the tumor.

In several cases of pigmented squamous cell carcinoma of the skin, metastatic foci in the lymphnodes also showed the presence of pigment blockade melanocytes [11,27,28]. However, melanin pigments within the cancer cells are extremely rare. JAUREGUI & KUNTWORTH[14] found ultrastructurally that melanin granules are present in variable numbers not only in melanocytes but also in neoplastic keratinocytes, Langerhans cells and macrophages in a case of pigmented squamous cell carcinoma of the cornea and conjunctiva. These pigments have also been found in neoplastic cells of spindle-cell carcinoma of the skin[29].

Aside from skin and oral tumors, melanocytes or melanin pigmentation have been described in epidermotropic carcinoma[30], breast carcinoma[31], odontogenic tumors[32,33] and salivary gland tumors[34,35].

Langerhans cells constantly locate not only in the mucosal epithelium of the esophagus[36–38] and uterine cervix[39], but also in skin appendages[40], dermis [41–45], lymphnodes[46–53] and thymus[54–56]. These cells are characterized ultrastructurally by Langerhans cell or Birbeck granules[57], and immunohistologically by Fc and C3 receptors[58,59] and B-cell-allo- and Ia-antigens[59–63]. Reports on proliferating cells with Langerhans cell granules in histiocytosis X[64], reticulum cell sarcoma[42], monocyctic leukemia[65] and malignant fibrous histiocytoma[66] stimulated the hypothesis that Langerhans cells may originate from mononuclear phagocytes[58], and constitute a reticuloepithelial system analogous to the reticuloendothelial system[67]. Langerhans cells have been observed in experimentally induced squamous metaplasia of the trachea and urinary bladder in vitamin A deficient rats[68]. These cells have also been identified in several adnexal tumors [42,69,70]. With the exceptional case of a bronchiolar-alveolar tumor of the lung [71] and a pleomorphic adenoma of the submandibular gland[72], Langerhans cells have never been found in a tumor of non-epidermal origin.

Merkel cells contain numerous neurosecretory granules that may liberate a transmitter substance across the synapse-like cleft between cells and adjacent nerve fibers[73–75]. Functionally, these cells are supposed to have some neurosecretory activity and are now considered as a part of the APUD system[76,77], although no secretory polypeptide hormone has been identified in it until now. Merkel cells
are known to have increased in the lesion of oral aphthous ulcer[78]. Recently, DE WOLF-PEETERS et al.[79] suggested that cutaneous APUDomas previously diagnosed as carcinoid or trabecular carcinoma may possibly arise from Merkel cells.

Conclusions

We studied a typical case of pigmented squamous cell carcinoma of the tongue and three cases of oral squamous cell carcinoma containing pigment blockade melanocytes within the tumor nests. The possible role of non-keratinocytes such as melanocytes, Langerhans cells and Merkel cells in tumors and tumorous conditions is discussed by a review of the literature.

Note added in the proof: While this paper was in press, Langerhans cells have also been found in dermoid cysts of the ovary (SHAH et al.: J. cutaneous Pathol. 8:52–68, 1981) and in tumors showing squamous differentiation (SWEENEY & COONEY: Cancer 45:1516–1525, 1980; WOODWARD et al.: Arch. Pathol. 104:130–133, 1980; HAMMAR et al.: Ultrastructural Pathol. 1:19–37, 1980).

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