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Mini Review

Gazing into the Early Dissemination Process of Cutaneous Malignant Melanoma Cells

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Abstract

Sporadic cutaneous malignant melanoma (SCMM) represents one of the most dramatic skin cancers, and its incidence is steadily growing in Caucasian populations. A sustained relative epidemiological increase has been disclosed in young women during their childbearing ages. In this group of patients, the peritumoral skin was reported to lack obvious signs of repeated ultraviolet light exposures including boosted mottled subclinical melanoderma. The possible impact of endocrine disruptors was suggested. Angiogenesis and lymphangiogenesis associated with SCMM potentially influence the neoplastic progression of the primary tumor and its metastases. In some instances, both the microvasculature is correlated to the extent of the tumoral growth fraction. In addition, the vascular network corresponds to a migration path for the intravascular and perivascular metastatic spread. Accordingly, the analytical quantification of the microvasculature could help establishing a prognostic aspect of the SCMM progression. Fractals and spectral analyses of immunohistochemical sections help defining the microvasculature distribution. The benefit of using spectral analysis is discussed and the modalities of application of this analytical method are scrutinized.

Keywords: Melanoma; Angiogenesis; Spectral analysis; Image analysis; Gender; Fractal analysis; Melanoderma; Microvasculature

Introduction

Sporadic cutaneous malignant melanoma (SCMM) is a dramatic cancer at risk for releasing metastases in proportion to the thickness of the primary tumor. Early detection of SCMM appears critical to the survival of the patient because at advanced stages, the SCMM metastases dramatically impede survival. The current procedures for early diagnosis of SCMM include clever clinical examination by an experienced physician including an expert dermatologist in dermoscopy. In addition, non-invasive cyanoacrylate skin surface strippings [1,2], and a tissue biopsy are appropriate when dermoscopy suggests the presence of SCMM. A series of immunohistochemical and molecular clues help identifying distinct types and stages of SCMM [3–5]. In our experiences, about 30-40% of suspected lesions correspond to an early SCMM.

The process of malignant transformation, progression and metastasis of SCMM is only partially understood. Furthermore, tumor staging proves to be particularly complex due to its multifaceted nature [5–7]. SCMM tumors are regarded as heterogeneous populations of neoplastic melanocytes displaying temporary unrestricted growth patterns compared with ordinary cells [5]. The progressive thickening of any primary SCMM is accompanied by an increased expression of various proto-oncogenes contrasting with a decreased expression of putative tumor suppressor genes [8]. Clearly, the peritumoral stroma in SCMM exhibits changes in a series of cell phenotypes [9–11]. In particular, the microvasculature shows frequently prominent changes [12–16]. In addition, there is general agreement to consider that the SCMM progression and dissemination are related to the neoplastic cell proliferation [13,17,18].

Of note, gender disparities were reported in the incidence and outcome of SCMM [19–23]. In recent years, some clinical studies were focused on SCMM developed in women during their childbearing age [19–24]. This neoplasm has shown an increased epidemiologic incidence over the past few decades. The vast majority of these SCMM were of the superficial type without any obvious relationship with a large number of dysplastic melanocytic nevi. Signs of frequent and intense sunlight exposure were not disclosed by the extent in the mottled subclinical melanoderma [20,24]. A series of investigations pointed to a possible relationship linking the development of some of these SCMM and the women hormonal status including the possible influence of hormonal disruptors [20,24]. However, these aspects remain yet unsettled.

It is possible to differentiate and clearly quantify the SCMM shape, size, scalloped border, and variegated pigmentation using computerized morphometry as well as fractal and multifractal methods [25–27].

The primary aims of the present study were to revisit some analytical aspects of SCMM-related micro-angiogenesis and peritumoral keratinocyte melanosis using novel developments in fractals and spectral analyses. Particularly, some basic aspects and relationships are reported between SCMM progression and the host vasculature, and possible relationships are highlighted in gender influences between both SCMM amplification and proliferation, and SCMM microvasculature.

Morphometry of subclinical epidermal melanoderma

The ultraviolet light-enhanced visualization (ULEV) method

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conveniently discloses patterns of epidermal melanoderma induced by chronic ultraviolet light exposures [20,28].

At the site of SCMM, the size of the tumor, its axial symmetry, the border irregularity, the form factor can be assessed. In particular, fractal analysis is well suited for assessing the edge structure [25].

Fractal and multifractal analysis of angiogenesis

The peri-SCMM microvasculature shows large interindividual variations in its pattern of distribution and extent [29]. No gender differences were disclosed in these aspects. A relationship between angiogenesis and SCMM progression appears as clear evidence. The microscopic examination of SCMM with specific endothelial cell immunostaining suggests some differences in the distribution of the vascular staining [30]. In fact, the homogeneity of the tissue vascularization is variable, as well as the orientation of the blood vessels.

The possibility of extracting information was explored about the vessel distribution, performing a textural analysis on the grey level of histological sections by means of fractal characterization by both Fourier spectrum and multifractal analysis [29]. Distinct different patterns of vasculature were identified according to the vessel density and distribution. Irregular profiles of ramified vessels appeared at different ranges of the grey level and seemed randomly distributed on the plane of the sections.

Many biologic processes are known to be heterogeneous, especially in the oncologic field. Repartition of estrogenic receptors, ploidy or cellular proliferation is known to be heterogeneous, and the heterogeneity of these variables has been deduced from multiple measures sampled in different sites of the tumor. Although such evaluation does not represent a quantitative approach, it evokes the heterogeneity of the phenomenon. The same is true for angiogenesis among SCMM.

Spectral analysis

Objective quantification of blood vessels and lymphatics [30] potentially represents an assessment of prognostic value. Numerous studies were conducted, but some results are conflicting leading to complex interpretations. One of the difficulties resides in the choice of the method of quantification of the vessels. Fractal and spectral analyses open new horizons.

Diffuse reflectance spectroscopy is well suited for exploring optical biopsies [31]. Diffuse reflectance provides quantitative measures of the wavelength-dependent reduced scattering and absorption coefficient that relate to the tissue structure and function, respectively [32]. A reduced scattering coefficient corresponds to an inverse power law function of wavelength in the visible range, and depends on the scatter size and density [33]. The absorption coefficient of a tissue is a function of physiological parameters particularly including blood volume fraction, oxygen saturation, blood vessel size, and melanin concentration [34].

Growth of SCMM depends upon appropriate neoagnogenesis. Such a relationship is, however, not similar for all tumors. In other respects, the metastatic dissemination is potentially enhanced by such microvascular network as well as by a boosted lymphangiogenesis; the SCMM is a typical archetype for these cancers.

Discussion

The worldwide increase in epidemiological incidence of SCMM in Caucasians over the past decades is possibly genuine and/or related to multiple close screenings in individuals with light complexion. Obviously, the risk markedly varies according to the combination of both the ethnic skin pigmentation and individual behavior regarding ultraviolet light (UVL) exposure [35,36]. SCMM commonly occurs in young adults [36,37]. SCMM is generally more common in women than in men (sex ratio 2:1), but carries a better prognosis for affected women. In some Caucasian populations of Western Europe, the rising incidence of SCMM over the past decades has particularly affected young women [20,38–40]. The cause for such sex- and age-related SCMM risk remains presently unsettled. Environmental factors, including UVL exposure from the sun and tanning sun beds [40] could be suspected, but the role of some chemical xenobiotics, particularly hormonal disruptors, is not ruled out [41–44]. Tackling the causative origin of SCMM appears to be provided by fractal analysis of ULEV pictures of the peritumoral skin. Chronic exposure of the epidermis to UVL induces an increased production of melanin by melanocytes and its transfer to neighbour keratinocytes in each epidermal melanin unit. Such activation is responsible for the presentation of fain mosaic melanoderma (FMM), particularly evident in Caucasian skin.

The acquired discrete uneven skin pigmentation forming the FMM pattern is a hallmark of photoaging [30,45]. Once delivered by melanocytes to keratinocytes, melanin acts, in part, as a UVL filter. However, according to individual parameters, including the phototype, age, and previous cumulative UVL exposures, skin presents distinct FMM appearances [45]. The diverse patterns of age-related FMM is conveniently disclosed and magnified using computerized ULEV [45], a charge-coupled device (CCD) camera equipped with an internal UVL-emitting unit is suitable for precise quantification of the epidermal melanin content [1]. The increased contrast between the FMM and the rest of the skin is the combined result of (a) the greater reflection of UVL wavelengths than visible light by dermal fibers, and (b) the greater UVL absorption by epidermal melanin [22]. Any other UVL-absorbing or –reflecting structure interposed above the dermal fibrous networks likely will alter the ULEV reading. In previous observations, some individuals exhibit rare and discrete foci of nearly total depigmentation [19]; the focal amelanotic skin appears as white iridescent skin ivory spots.

Beyond regular morphologic parameters including tumor thickness and the proliferative rate, other prognostic markers might add important information improving prognosis, treatment and survival. Immunohistochemical markers, gene expression arrays, genomic hybridization and mutational profiling are possible. These methods require specially equipped laboratories. Fractal and spectral analyses can be added to the list helping improving SCMM classifications. Computerized analysis of SCMM achieves high sensitivity and specificity in diagnosis in the interpretations of pictorial data according subjectivity.

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