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Histological Alterations and Biochemical Markers of Skin Cancer: A Review

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Abstract

Skin cancer is a broad range of malignant and benign neoplasms that are common worldwide and more prevalent than many other cancer types. This condition involves the neoplastic proliferation of cells and tissues within the skin and can be associated with significant morbidity and mortality. This review summarizes the most recent advances regarding histopathologic changes and management of skin malignancy, which are classified by three types-Melanoma (MM), Basal Cell Carcinoma (BCC) Squamous Cell Carcinoma (SCC). They also show certain patterns of atypia, invasion and proliferative activity which is vital for histopathological diagnosis as well as prognostic stratification. Molecular changes demonstrate that mutations in BRAF (v-raf murine sarcoma viral oncogene homolog B1) or NRAS (neuroblastoma RAS viral oncogene homolog) in the RAS signaling pathway, Hedgehog family of proteins and β-catenin may underlie differences in clinical outcome as they affect tumor progression and response to therapy, particularly in skin cancers. In recent years, encouraging results have been observed in the treatment of HCC through targeted therapies and immune checkpoint inhibitors as first- or second-line treatment objectives, resulting in improvement in the clinical outcomes of patients with HCC. However, these strategies are also faced with formidable challenges for clinical translation due to cancer-relapsing therapeutic resistance and tumor heterogeneity. Tumor microenvironmental [practices] like Ti [tumor infiltrating]

immune cells, interaction with (the)extracellular matrix are also key to the tumor development and progression. High throughput technologies like molecular profiling and precision medicine provide new treatment markers as well as the means to individualize therapy. However, skin cancer represents one of the most heavily treated malignancies, especially with advanced disease. This would, in turn, integrate lithologic, molecular and therapeutic data into the diagnostic inferences standardized for patients—improving understanding & rational of treatment thereby enabling better reporting of outcomes.

Keywords: MM, BCC, SCC, Skin Cancer, EGFR amplification

Introduction

Skin cancer is a nonspecific term for one of the widest ranges of malignant and benign neoplasm that are frequent worldwide, the most common neoplasms in many countries ranked by incidence prior to clonal malignant tumors. It is characterized by neoplastic proliferation of cells and tissues within the skin, which may lead to considerable morbidity and mortality. Ultraviolet (UV) radiation is one of the main etiologic factors for most subtypes of skin cancer, including basal cell carcinoma, squamous cell carcinoma and melanoma. These cancers may present with varying clinical features and often require evaluation through a skin biopsy and histopathological assessment to determine the specific type. This heterogeneous group of neoplasms may require a skin biopsy with histopathological evaluation and advanced therapies, including topical treatments, local non-topical therapies (eg, antineoplastic injections), systemic medications (Hussein et al., 2025). Increased exposure to ultraviolet (UV) radiation, population ageing, and lifestyle and environmental changes that have occurred over the last few decades are believed to be major factors contributing to the global increase in the incidence of skin cancer (D'Orazio et al., 2013).

Histopathological examination is a gold standard for accurate diagnosis and a better prognostic evaluation of the patient. As THA is a known predictor of prognosis, staging the malignant tumors in excision biopsy specimen must be stressed upon. Although and pass clinically pen are no more frequently misidentified peels malignantly than vegetable but nevertheless be pigmented, ectopic, or, at times, ulcerated, biopsy specimen should therefore be subjected to histologic scrutiny to amend definitive diagnosis. Thus, skin biopsy must be the gold standard for the definitive diagnosis and prognostic classification of the subject. An appreciation of histopathological patterns assists in prognosis & guiding the management effectively (Thapa et al., 2018).

Melanoma lesions show distinctive architectural and cytological features. Architecturally and irregularly shaped, asymmetrical with contoured edges and inconsistent coloration. Tumor size is the minimal factor, along with cellular pleomorphism, nuclear atypia, ulceration, and mitotic activity. Due to molecular heterogeneity, melanoma has varieties of molecular subtypes with distinct clinical behaviors and therapeutic responses (Müller & Reichrath 2014; Puckett et al., 2024).

Basal cell carcinoma (BCC) is the most common skin cancer and frequently presented malignancy in the USA with nearly 1 of 5 Americans being affected during their lifetime. Although BCC is clinically non-fatal, it is a locally invasive malignant neoplasm that invades and destroys surrounding tissue, and can result in significant local morbidity and cosmetic deformity, particularly in, but not limited to, the head and neck (face, ears, and periocular region). If identification and management are delayed, ulceration and disfigurement or recurrence can occur, indicating the importance of stated psychosocial dynamics (Puckett & Steele, 2025). These tumors show a different degree of keratinization and cellular differentiation, and poorly differentiated tumors are more likely to metastisize, similar to squamous cell carcinoma. Such differences have important implications as well for histopathological classification important for management clinically (Koyuncuer, 2014).

In contrast, melanoma displays considerable histological heterogeneity that encompasses the superficial spreading, nodular, lentigo maligna and acral lentiginous melanoma subtypes. Each of these subtypes is associated with distinctive morphological features and clinical outcomes, highlighting the importance of precise histological evaluation. Additionally, for certain diagnoses, immunohistochemical markers (such as S100, Melan-A and HMB-45) are invariably employed to confirm melanocytic origin beyond histology (Hussein et al., 2025).

Skin cancers have been clinically recognized for over a century but it is only now that advances in our understanding of the pathogenesis of these malignant processes have defined their molecular pathology. Genetic aberrations (BRAF and NRAS mutations in melanoma or constitutive activation of the Hedgehog signaling pathway in basal cell carcinoma). These developments have created new targets for targeted therapy that are among the leading management strategies for patients with advanced skin neoplasms. Combination of histopathological findings with molecular & immunohistochemical data has also enhanced diagnostic and prognostic potential (Winter et al., 20226) Besides,

Skin cancer management relies on the nature, stage and histological characteristics of the malignant tumour. Surgical excision is mainly used for localized lesions and advanced cases are typically treated with radiotherapy, chemotherapy or targeted/immunological therapy in combination. Importantly, as compared to ten years ago where only palliative treatment was conducted, immune checkpoint inhibitors and targeted agents have dramatically changed the spectrum of care in patients with metastatic melanoma, giving rise to a multitude of options. Despite advances in immune-oncology, significant barriers remain for the treatment of resistant disease and its recurrence, necessitating further exploration of innovative strategies (Sol et al., 2024).

Classification of Skin Cancer

The most common types of skin cancer are cutaneous malignant melanoma and non-melanoma skin cancer (NMSC), which also may be further subdivided based on histopathological features, staging criteria or molecular characteristics. Basal cell carcinoma (BCC), squamous cell carcinoma (SCC] and Merkel cell carcinoma (MCC) are all types of non-melanoma skin cancer (NMSC). These tumours are broadly distributed clinically as well as in their biological progression. Deregulation of the Hedgehog pathway is a common finding in BCC, while SCC and MCC are defined by their extremely high mutational and neoantigen burden (Que et al., 2018).

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Squamous cell carcinoma; Second most common skin cancer in the US; Incidence of SCC rises consistently each year and constitutes a public health problem. Mortality rates of cutaneous squamous cell carcinoma rival melanoma, renal carcinoma, and oropharyngeal carcinoma in central and southern United States. Surveillance, diagnosis and treatment need to be undertaken urgently so as to reduce potentially significant morbidity and mortality risks. While surgical excision is the backbone of therapy, active research delivers new therapeutic modalities (Combalia & Carrera, 2020; Hadian et al., 2024).

Melanoma is now recognized as a malignant tumor associated with complex histological subtypes that differ in clinical behavior and prognostic significance. The most common sub-types are superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma and acral lentiginous melanoma. The vertical growth phase of nodular melanoma with a subsequent vertical growth pattern is much briefer, and this variable has an important impact on prognosis compared to all other types of superficial spreading melanoma. (Acral lentiginous melanoma): This is the other presentation and is more common in darker-skinned populations, tends to be diagnosed at later stages than compared to nodular melanoma and commonly occurs on the palms, soles and nail beds (Swetter et al, 2019).

In addition to histological categorization, skin cancers are staged using standardized systems of assessment, the most characterized being the Tumor–Node–Metastasis (TNM) framework by American Joint Committee on Cancer (AJCC). Every individual has an own T M N grade for every staging the dignity is on the base of size, regional nodes involvement and distal metastasis; And For instance, in melanoma imaging Breslow thickness and ulceration status are both staging and prognostic variables. Researchers used staging to help guide treatment decision-making and also accurate prognostication of overall survival (Gershenwald et al., 2017).

As an example, one of its additional domains of classification is risk stratification for non-melanoma skin cancers. Based on clinical and pathological characteristics and molecular features, tumours may often be grouped into risk categories that are either low or high Risks. Risk factors. This includes; large tumor size, poorly defined borders, recurrent lesions, located in an immunocompromised host and/or high risk anatomical area (i.e. face or ears). This classification assists clinicians in determining how to proceed with treatment, whether the patient should undergo more aggressive therapy or requires more intensive follow-up (Que et al., 2018).

With molecular biology blossoming like no other science in the last few years, we have to now cope with a new order of classification at genetic and molecular level. One example is BRAF mutation, which is observed in ~50% of melanomas and has clinical/therapeutic implications. It is also frequently seen in basal cell carcinoma as a consequence of alteration of Hedgehog

signaling. Therefore, molecular classification represents a progression towards studying the biology of tumors and targeting the development of personalized medicine approaches for treatment (Di Nardo et al., 2021).

Histological Alterations of Skin Cancer

While histopathologic evaluation remains the diagnostic gold standard in skin cancer, it also conveys valuable information regarding tumor type, biologic behavior, and prognostic factors. Skin cancers arise from distinct cell lineages in the skin), and the monochromatic nature of their histopatological examination correlates with the molecular and pathological processes involved in tumorigenesis. Basal, Squamous and Melanoma are malignant skin tumors and their histology morphology or changes can hardly be determined by routine biochemical and histopathological methods to make precise diagnosis for the best treatment of the disease (Paolino et al., 2017).

Basal cell carcinomas (BCCs) are a group of malignant tumors from the epithelial cells of either epidermis or hair bulge stem cells, composed atypical basaloid elements with relatively little cytoplasm and hyperchromatic nuclei organized in variable size nests and strands yield an H&E-stained blue-cell appearance consistent for this tumor. Peripheral palisade, stroma fibromyxoid changes and cleft artifacts are common in neoplastic aggregates. Other shared characteristics include brisk mitotic activity, apoptotic cells, necrosis, calcification, keratin-derived amyloid deposition in the dermis and superficial ulceration with pigmentation (due to colonic melanocytes and/or dermal melanophages). No precursor lesions are identified, but a background of solar elastosis is virtually uniformly present (Sergi et al., 2025). Although the nodular BCC is obviously well circumscribed and far less invasive, infiltrative and morpheaform types show tortuous strands of tumor cells extending into the deep dermis with greater risk of recurrence. Those variations in nodular BCC indicate that histological assessment is the best actual predictor of tumor behavior (Marzuka & Book, 2015; Saldanha et al., 2003).

Comprising the keratinocytes, squamous cell carcinoma has a broad histological differentiation scope. The biomicroscopic features of the studied specimens have been confirmed in the literature, where it was shown that well-differentiated SCC is characterized by keratin pearl formation, intercellular bridges and a relatively preserved cellular architecture; and poorly-differentiated SCC: severe cellular atypia, high mitotic Figure, keratinization absence (Gonçalves Ferreira et al., 2021). CNew: cSCC can complicate metastatic disease. Most commonly lymph nodes are the metastatic sites, but involvement with metastases can also be present in lung, bone, brain and mediastinum. Histopathological parameters that may be associated with an increased risk of metastasis include a deeper skin invasion, leasons greater than 2 cm in size and perineural invasion. Thus, effective management of this malignancy is heavily reliant on an accurate histopathological diagnosis (Fania et al., 2021; Que et al., 2018).

As such, melanoma has emerged as the most histologically diverse of all skin cancers and this mirrors its patchy pathogenesis. This is the most malignant type of skin cancer which develops from melanocytes and characterized by asymmetry, irregular borders, cytological atypia and pagetoid spread of atypical melanocyte upwards in epidermis. Breslow thickness, which is a measure of the depth of invasion of a melanoma and has been established for several decades as one of the strongest prognostic predictors in melanoma (Caravielloet al., 2025) (ii) Other clinicopathological variables such as ulceration, mitotic rate and tumor-infiltrating T-lymphocytes. Though melanoma subtypes demonstrate several different forms of histology (eg, radial growth phase [superficial spreading melanoma vs no radial component vertical growth only, nodular melanoma] (Gershenwald et al. 2017)

IHC is not only routine but also an important part of diagnosis, differential diagnosis, and confirmation of tumors. Melanoma was positive in the cytokeratin stains (epithelial origin) like S100, HMB-45, Melan-A, and together with SCC recent markers observed as Ki-67 (proliferation) and p53, ap53 together with tumors suppressed by modified gene factors. Also, these markers provided additional insight into tumor biology and aggressiveness (Voiculescu et al., 2025).

The histological changes appear to closely correlate with accompanying mutations and dysregulated signaling pathways at the molecular level. A famous example is BCCs, which have a strong correlation with changes in the Hedgehog signaling pathway via mutations in PTCH1 gene (Di Nardo et al., 2021). In melanoma, for example the ubiquitous mutations of regulating excessive cellular proliferation and survival through BRAF and NRAS. Initially neoplastic, increased mitotic activity and cellular atypia in morphology and molecular pathology are closely associated with each other, which also corresponds to the histological changes related to these molecular alterations (Pizzichettaet al., 2025).

The lack of gestational hypertensive disease progression and histological alteration underlines not only the interaction with the tumor cell micro-environmental but one more fundamental

hallmark of cancer [2]. The influence of the tumor stroma (comprising predominantly fibroblasts, immune cells, and components of the extracellular matrix (ECM)) on cancer progression. Nevertheless, inflammatory infiltrates (particularly the affection of lymphocytes) are also observed in melanoma, and may reflect an active anti-tumour immune response (Swetter et al., 2019). Conversely, immune suppressive micromilliue also can support tumor development and treatment resistance. Angiogenesis is another important histologic feature of late stage tumours that provides the neoplasm with increased perfusion and the ability to grow and subsequently metastasize (Stockmann et al., 2014).

With the development of digital pathology and digital image analytic techniques (referred to as computerized histology) associated with machine learning or other AI methodologies, it has become possible to objectively quantify certain features of tumors. These tools help to quantify our patterns, define provisional differentiators and give users specificity. Advances are also ongoing toward customized medicine where therapeutic approaches can be tailored based on unique tumor traits connection histopathology with molecular profiling (Figure 1).

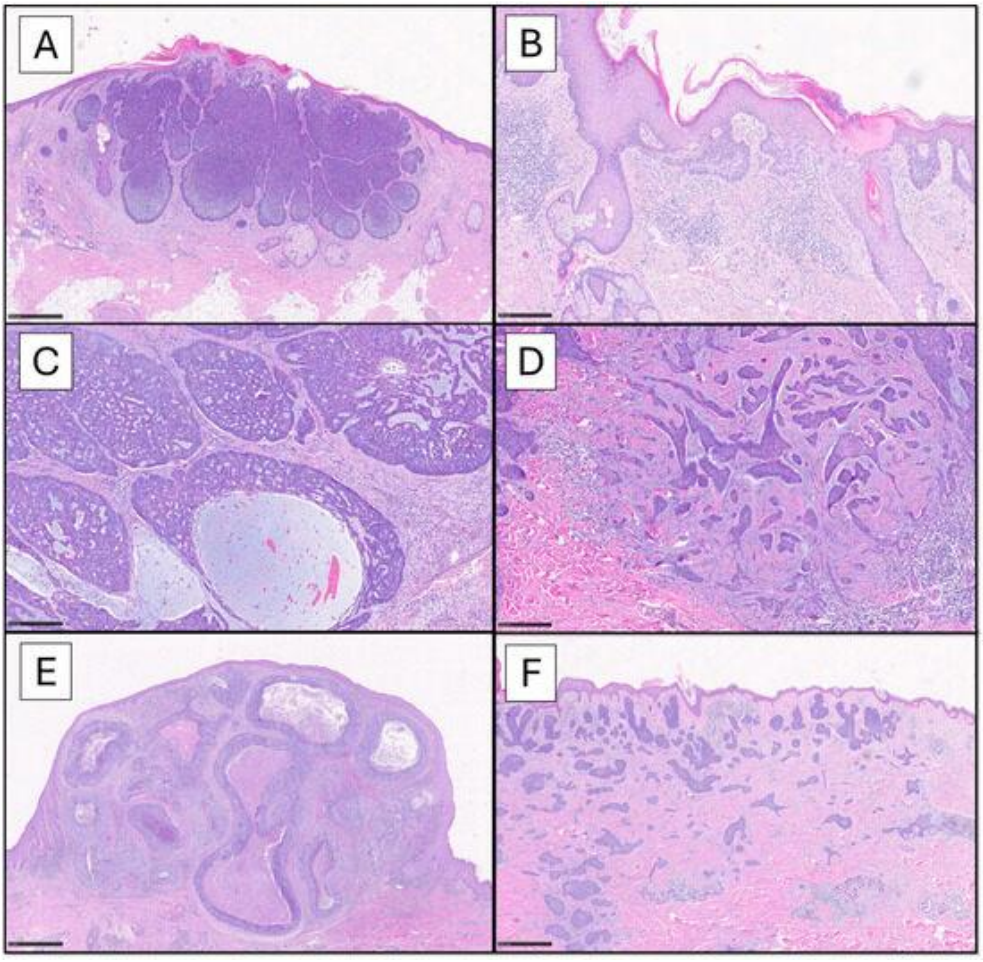

Figure 1. This figure shows the more common BCC histotypes we may encounter in practice more frequently. The nodular pattern is characterized by localized proliferation of large nests, with architectural diversity from solid ((A), scale bar 500 µm) to adenoid-cystic ((C), scale bar 250 µm) to frankly cystic (nodulocystic, (E), scale bar 1 mm); stromal myxoid changes particularly affect the centers of the nests (C). Superficial pattern ((B), scale bar 250 µm) is characterized by neoplastic cell buds assorting from the basal layer of the epidermis nestled in the papillary dermis Infiltrative pattern ((D), scale bars 250 µm) shows arrows of atypical basaloid cells, with spiky projections, brushing however within a fibromyxoid and desmoplastic stroma. Figure 1: Micronodular variant ((F), scale bars = 500 µm by small nests diffusively infiltrating the dermis with unclear margins (Hematoxylin-Eosin 4x-20x) (Sergi et al., 2025).

Therapeutic approaches for skin cancer

The available treatments for basal cell carcinoma (BCC) of the skin include excision, radiation therapy, cryosurgery, electrodesiccation and curettage; photodynamic or laser-beam light exposure; and topical therapies. Each of these strategies has a place in targeted clinical situations. These have 85 to 95% recurrence free rates (depending on case selection) But that is way better than the surgery because it has the better cure rates with BCC and SCC (Hasan et al., 2023; Shokrollahi et al., 2014).

This process consists of excising the cancer tissue and surrounding non-cancerous skin. This guarantees that there are no more cancer cells It also allows a lesser-known technique in which surgeons check the tissue removed to be sure no cancer is left behind. Surgery is highly effective used for BCC and SCC as it can conform to the size of the tumor and its position. This minimizes the potential for recurrence of cancer while sparing healthy tissue and organ function. Basal cell carcinoma and squamous cell carcinoma are sometimes surgically removed. What does BCC look like BCC appears as a small bump (shiny or slightly depressed) or pink patch in skin. It most typically occurs on sun-exposed areas (Sutrisno et al., 2025). Such surgery allows the immediate assessment of histological margins while completely excising surrounding healthy tissue or the tumor. The cure rate and recurrence aspect of MMS has higher credibility than SD in high or recurrent tumors. In melanoma, wide local excision is performed based on tumor thickness with margins depending on clinical practice guidelines (Swetter et al., 2019).

Radiotherapy is an integral part of systemic therapy, either specifically or collectively with surgery in patients who are unsuitable for surgical candidates or when tumours exist at anatomical locations that make resection increasingly challenging. Has very high local control and used for SCC and select BCC However, this is rarely applied to melanoma due to the fact that melanocytic tumors have relative radioresistance, but palliative or brain metastases are possible (Fabian et aal., 2020). Topical therapies and much more minimally invasive approaches are being used for less deep and lower risk lesions. Topical agents suitable for superficial BCC include 5-fluorouracil (5-FU) and imiquimod, also available for actinic keratosis, a precursor of SCC. These therapies work through mechanisms that specifically target cytotoxic attack or enhancement of local immunity. In addition, photodynamic therapy (PDT) employs a light-activated photosensitizer specifically targeting tumor cells. This may be an acceptable treatment for superficial lesions, but PDT offers good cosmetic results (Tan et al., 2023).

The introduction of target therapy have revolutionized the treatment in advanced and metastatic skin cancers, especially melanoma. The mutation of BRAF gene is prevalent in many melanomas, the V600E mutation being the most common. Vemurafenib and dabrafenibClass: Selective mutant BRAF inhibitorsMolecular mechanism: Induces extreme tumor regression (caused by inhibition of mutant BRAF) In this way, these agents are given with MEK inhibitors (e.g., trametinib) to increase efficacy and reduce resistance (Gershenwald et al. Also BBCC is frequently associated with alterations of the Hedgehog signalling pathway, for this reason vismodegib and sonidegib are useful compounds in locally-advanced/in-operable disease (Di Nardo et al., 2021). Immunotherapy has been one of the breakthroughs in therapy for melanoma, and indeed for skin cancer overall. A few new treatment options that significantly enhance survival result (Wang et al., 2025) include PD-1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)-targeting immune checkpoint inhibitors. A) immune checkpoint inhibition including agents such as nivolumab, pembrolizumab, and ipilimumab enhances tumor cell immunity. Immunotherapies have improved the prognosis of advanced melanoma patients and many can produce long-lasting complete remissions in individuals. The other aspect is immunotherapy, which is increasingly studied in SCC, especially for advanced or metastatic disease (Swetter et al., 2019).

Chemotherapy has long been the standard of care for advanced skin cancer, but is now becoming an infrequent first-line treatment due to the increasing use of less toxic and more effective targeted and immunotherapeutic therapies. However, it still remains available for restricted use when other treatments are not feasible. Therapies based on biomarker-driven targets, also known as molecular and genetic profiling of tumours, appear to be a therapeutic direction worth further exploration. Proposed biocaners include PD-L1 expression, tumor mutational burden and genetic mutations for patient identifiers for those who would benefit from immunotherapy and targeted therapies (Modrakowska et al., 2020). This tactic is in accordance with principles of precision medicine that tries to optimise therapeutic effect, whilst wanting to decrease adverse side effects. In systemic therapy, systemic therapies, including chemotherapy and biologicals and immunotherapy (IT), are the mainstay of cancer treatment, while supportive and adjunctive therapies are meant to be employed complementary to systemic therapy. The therapeutic component is restricted to management of pain, wound and psychological advices at best health state. Nevertheless, sun safety & screening, and patient education – fundamentals of efficient prevention of skin cancer burden, also

are effective tools irrespective of development of the new drugs©2019 Aidem Health, Inc.

This would encompass new platforms such as artificial intelligence and digital health technologies enabling more precise diagnosis. This helps in better detection of lesions, risk stratification and monitoring of response to treatment. Although treatment for skin cancer has advanced significantly, there are still challenges to overcome (including resistance to therapy, adverse effects and limited access to novel therapies). Even these limitations hold huge possibilities to develop new pharmacological agents, combination approaches and personalized therapies by specialists (Zhou et al., 2025).

Conclusions

Skin cancer (SC) Skin cancer is a heterogeneous group of cancers and a worldwide epidemic. It is categorized into two major types: melanoma skin cancer (MSC) and non-melanoma skin cancers (NMSCs). These cancers account for >90% of all skin cancers. Histopathological evaluations are a crucial step for skin cancer diagnosis, management plans, etc., but inherently focus on tumor biology and grading/staging. The epidermal truly Markers have additionally modified the pattern diseases will recover changed into analyzed and handled in. Localized disease has traditionally been treated by surgery but there have been significant advances in systemic treatment for advanced disease with the advent of chemotherapy and immunotherapy with personalized medicine. But this hopeful prospect is accompanied by a challenge in timely diagnosis and treatment resistance. It is therefore better management and prognosis of skin cancer patients using integration of histological, molecular and clinical data.

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