DIFFICULT TO DIAGNOSE SQUAMOUS CELL CARCINOMA: A LITERATURE REVIEW AND A CASE REPORT

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Abstract: Squamous cell carcinoma (SCC) is the second most common type of skin cancer, right behind basal cell carcinoma (BCC), arising from the keratinocytes of the epidermis. It is typically associated with cumulative ultraviolet (UV) exposure, especially in childhood and youth. In recent years, immunosuppression, as therapeutic approach, has emerged as an increasingly important contributor to tumorigenesis, and the appearance of SCC in areas of chronic inflammation must also be kept in mind. While SCC is usually straightforward diagnosis due to its characteristic clinical presentation, some variants of SCC can be difficult to diagnose. These "difficult-to-diagnose" SCCs may present with atypical features, mimic other dermatological conditions, or arise in non-sun-exposed areas, leading to diagnostic challenges and delays in treatment. This paper discusses the clinical and histopathological features that complicate the diagnosis of SCC, with an emphasis on specific SCC subtypes and diagnostic techniques. We also present a case report of Bowen's disease in a 78-year old patient.
Keywords: Squamous Cell Carcinoma (SCC), Bowen's Disease, Dermoscopy, Histology

1. INTRODUCTION

Squamous cell carcinoma (SCC) is the second most common malignancy of the skin after basal cell carcinoma. Rates of mortality for squamous cell carcinoma are comparable to those of melanoma, renal carcinoma, and carcinoma of the oropharyngs. Pathological variants of SCC include: verrucous SCC, spindle cell SCC, desmoplastic, acantholytic and adenosquamous variants. Timely surveillance, early diagnosis, and prompt treatment are crucial to minimize morbidity and mortality risks. Moreover, challenging cases often require the integration of advanced diagnostic tools, including immunohistochemistry, molecular testing, and imaging, to differentiate SCC from other entities. This paper aims to explore the complexities involved in diagnosing difficult cases of SCC, highlighting the clinical, histopathological, and molecular factors that contribute to diagnostic uncertainty, and discussing emerging diagnostic techniques that may aid in improving accuracy. Here, we also present a case of Bowen's Disease clinically presenting as erythematous patch on the foot.

2. MATHERIAL AND METHODS

The literature search was conducted using several databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search included articles published between 2010 and 2024, using keywords such as "squamous cell carcinoma (SCC)", "clinical variants of SCC", "histology of SCC" and "diagnosis of SCC". Boolean operators (AND, OR) were applied to refine the search results. In this report we represent the case of a 78-year old patient who was diagnosed and treated at the Dermatology and Surgery Department of Clinical Hospital Stip, North Macedonia.

3. RESULTS

LITERATURE REVIEW

Clinical Variants of Difficult-to-Diagnose SCC

SCC in Situ (Bowen's Disease)

Bowen's disease (BD) is an in-situ squamous cell carcinoma (SCC) of the epidermis. The main etiological factors of BD include ultraviolet light exposure, immunosuppression, and papilloma virus infections. Other conditions, such as thermal injury, ionizing radiation, chronic lupus erythematosus, lupus vulgaris and ultraviolet-A exposure, make grater possibility of arising of BD of the damaged skin. Bowen's disease represents the earliest form of SCC, where malignant keratinocytes are confined to the epidermis. The appearance of a large group of flat epithelial cells without keratin production in the dermis favours the progression into invasive SCC. The condition can be difficult to diagnose due to its nonspecific appearance. Bowen's disease can clinically mimic vast majority of diagnoses like: actinic keratosis, BCC, SCC, lichen planus, nummular eczema, discoid lupus erythematosus, lichen planus, seborrheic keratosis, psoriasis, Paget's disease. Bowen's disease typically presents as solitary, asymptomatic, slow-growing, well-demarcated, erythematous, scaly patch, but it can vary in colour and texture, leading to confusion with benign conditions. Diagnosis often requires a biopsy to confirm the presence of atypical keratinocytes throughout the full thickness of the epidermis.

Desmoplastic SCC

Desmoplastic SCC is a rare, fibrous variant of SCC characterized by an intense desmoplastic stromal response. This variant can be challenging to diagnose both clinically and histologically. Desmoplastic SCC often presents as a firm, indurated plaque or nodule that may lack the typical ulceration or scaling seen in conventional SCC. Desmoplastic SCC is rare but its clinical significance arises from the increased risk of local recurrence and metastasis. Histologically, it is characterized by elongated cords of atypical, spindle-shaped, epithelial cells associated with desmoplastic stroma, surrounded by dense collagen, which can make it difficult to distinguish from other fibrous or spindle-cell tumors like desmoplastic melanoma, atypical fibroxanthoma, dermatofibrosarcoma protuberans, and other sarcomas.

Pigmented SCC

Pigmented squamous cell carcinoma (PSCC) is described as a rare variant, characterized by proliferation of atypical squamous cells with formation of horn pearls permeated by dendritic melanocytes. The main clinical and histological differential diagnoses of PSCC are: pigmented seborrheic keratosis, melanoacanthoma, pigmented pilomatricoma, pigmented actinic keratosis, pigmented Bowen's disease, pigmented basal cell carcinoma, melanoma. The pigmentation in these tumors can obscure their typical SCC features, making dermoscopic evaluation and clinical examination more challenging. This variant requires careful differentiation from malignant melanoma, particularly in pigmented lesions arising on sun-damaged skin.

SCC of the Nail Unit (Subungual SCC)

Subungual SCC is a rare tumour, which arises from the nail bed and matrix, where it clinically presents with painful subungual hyperkeratosis, onycholysis, and nail deformity. Subungual SCC has different clinical presentations which can imitate benign or malignant nail lesions, therefore it is called "the great mimicker nail tumour". Pain, inflammation and swelling is usually associated with invasive SCC and involvement of the underlying bone. Subungual SCC is frequently misdiagnosed as a chronic fungal infection, wart, or trauma, pyogenic granuloma, longitudinal melanonychia, subungual exostosis, onychomycosis, onychopapilloma, chronic paronychia, fibrokeratoma, and onychomatricoma. It may manifest as a painful, thickened nail or ulceration, and the subtle nature of the changes can lead to delayed diagnosis until the lesion becomes advanced.

SCC in Non-Sun-Exposed Areas

Although SCC is classically associated with sun-exposed skin, it can develop in non-sun-exposed areas such as the oral cavity, ano-genital region, and mucous membranes. These cases can be difficult to diagnose as they often lack the typical clinical clues seen in UV-induced SCC. SCC in these regions can present as erosions, ulcers, or persistent plaques, and may mimic inflammatory or infectious conditions, such as lichen planus, aphthous ulcers, or condyloma.

Histopathological Challenges in Diagnosing SCC

Well-Differentiated SCC

Histologically, SCCs are classified into 4 degrees of differentiation: well differentiated (G1), moderately differentiated (G2), poorly differentiated (G3), and undifferentiated (G4). This classification is based on their degree of keratinization, nuclear atypia and histological architecture. Well-differentiated SCC can be difficult to distinguish from benign lesions such as keratoacanthoma or seborrheic keratosis. Typical SCC has nests of squamous epithelial cells arising from the epidermis and extending into the dermis. The malignant cells are often large with abundant eosinophilic cytoplasm and a large, often vesicular, nucleus. Variable keratinisation (keratin pearls etc.) is present.

Well-differentiated SCCs retain many features of normal keratinocytes, including squamous differentiation and keratin production. Clinically, well-differentiated SCC presents as a raised, nodule with crust that can be mistaken for benign keratotic lesions.

Acantholytic SCC

Acantholytic squamous cell carcinoma (aSCC) is considered as a high-risk variant of SCC. Acantholytic SCC as a histopathological variant is characterized by acantholysis, leading to a pseudo-glandular or pseudovascular pattern. This histologic pattern can lead to mistakening the lesion as a benign blistering disorder or a vascular tumor. The acantholytic pattern may mask the invasive nature of the tumor, leading to underestimation of the lesion's malignancy.

SCC with neurotropism

SCC with neurotropism invades peripheral nerves, which can result in significant morbidity due to nerve involvement. This variant can be difficult to diagnose due to its atypical clinical appearance, which may resemble a scar, and because it often lacks the characteristic ulceration or scaling of typical SCC. Histologically, the tumor cells infiltrate nerve fibers, which may be overlooked on routine histopathological examination.

Diagnostic Techniques

Diagnostic techniques which aid in the identification of SCC include: dermoscopy, histopathology, molecular diagnostics, imaging. Dermoscopy can aid in the identification of SCC, particularly in cases where the lesion mimics other conditions. Key dermoscopic features of SCC include keratin masses, hairpin vessels with white halos, ulceration, and the presence of blood spots. In some difficult-to-diagnose cases, dermoscopy can help distinguish SCC from benign or inflammatory conditions by highlighting these specific vascular and surface features.

Histopathological examination remains the gold standard for diagnosing SCC. A biopsy should be performed when clinical or dermoscopic features raise suspicion of SCC, particularly in difficult-to-diagnose cases. Special techniques, such as immunohistochemistry, can be used to differentiate SCC from other mimicking tumors like melanoma or basal cell carcinoma.

In cases where histopathological differentiation is challenging, molecular diagnostic techniques, such as p53 mutation analysis or immunohistochemical staining for markers like cytokeratins, can assist in confirming the diagnosis of SCC and ruling out mimickers.

For advanced or difficult-to-diagnose cases, imaging techniques such as ultrasound, MRI, or CT scans may be used to assess the depth of invasion, particularly in subungual SCC or SCC with neurotropism.

4. CASE REPORT

We present the case of a 78-year old woman with a scaly patch on the dorsal side of her right foot, which was present there for few years. The patient was with skin photo type Fitzpatrick 2, with negative family and personal anamnesis for skin cancer. Skin was not photo damaged, she worked as a teacher, without outdoor activities. Macroscopically the lesion was scaly pink patch, 20x30mm in dimension (Fig.1). A dermoscopy examination was performed with finding of white scales, dotted vessels, with linear arrangement, predominantly on the peripheral part of the lesion (Fig.2 and Fig.3). Few differential diagnoses were taken into consideration: Mb.Bowen, SCC, discoid lupus erythematosus. Total excision was performed, and the histology finding confirmed the diagnosis of Bowen disease. The presence of clustered glomerular vessels is a highly accurate dermoscopic criterion in differentiating, rapidly and efficiently, BD from other forms of SCC, and may enhance the clinical diagnosis of BD in everyday practice.

Fig.1 *Macroscopic appearance of the lesion: scaly pink patch, 20x30mm in dimension*
Fig.2, Fig.3 *Dermoscopic findings of white scales, dotted vessels, with linear arrangement*

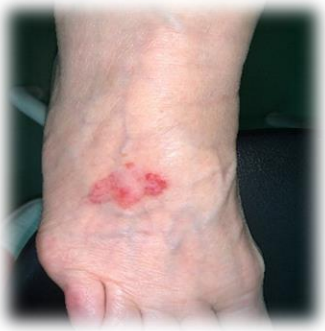

Fig.1

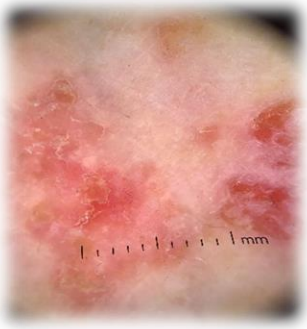

Fig.2

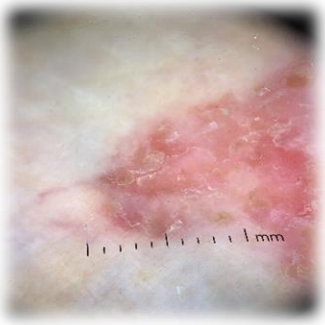

Fig.3

4. CONCLUSION

Squamous cell carcinoma can be difficult to diagnose in certain clinical and histopathological scenarios due to its ability to mimic benign, inflammatory, or other malignant conditions. The variants of SCC discussed in this report, including SCC in situ, desmoplastic SCC, and pigmented SCC, pose unique challenges in diagnosis due to their atypical presentations. A thorough understanding of the clinical, dermoscopic, and histopathological features of these difficult-to-diagnose SCCs is essential for accurate diagnosis and timely treatment. Our case report emphasises the importance of dermoscopy in diagnosing and treating Morbus Bowen in timely manner. Biopsy and histopathological examination remain the cornerstone of diagnosis, supported by dermoscopy and molecular techniques where necessary. Early and accurate identification of these variants is crucial to prevent delayed treatment and to improve patient outcomes.

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