



Clear Cell Variant of Squamous Cell Carcinoma: A Comprehensive Review of Pathogenesis, Diagnosis, and Management

¹Dr. Asvini T P, ²Dr. Keerthana G, ³Dr.Mathumala Subramanian,
⁴Dr. Marytresia Jeyapriya S, ⁵Dr.Sathish Kumar M

¹ CRI, ^{2,3}Post Graduate, ⁴Professor, ⁵Head of the Department
Department of Oral and Maxillofacial Pathology
Karpaga Vinayaga Institute of Dental Sciences
Chengalpattu, India

Abstract

Clear Cell Variant of Squamous Cell Carcinoma (CCSCC) is a rare histopathological subtype of squamous cell carcinoma characterized by the presence of tumor cells with clear cytoplasm. This variant has been reported in cutaneous as well as mucosal sites, including the oral cavity, cervix, and lungs. The clear cell morphology is primarily attributed to intracellular accumulation of glycogen, lipids, or hydropic degeneration. Due to its rarity and overlapping histological features with other clear cell neoplasms, CCSCC poses significant diagnostic challenges. Accurate diagnosis requires careful histopathological evaluation supported by special staining and immunohistochemistry. The biological behavior of CCSCC remains under investigation, although some studies suggest it may exhibit aggressive characteristics. Treatment strategies are similar to conventional squamous cell carcinoma and include surgical excision, radiotherapy, and systemic therapies in advanced cases. This review aims to provide a detailed overview of CCSCC, including its etiology, pathogenesis, histopathology, clinical features, diagnostic approaches, and management strategies, supported by current literature.

Keywords

Clear Cell Squamous Cell Carcinoma, Clear Cell Variant, Oncology, Skin Cancer

Introduction

Clear Cell Variant of Squamous Cell Carcinoma (CCSCC) is an uncommon morphological subtype of squamous cell carcinoma characterized by tumor cells exhibiting clear cytoplasm. This feature distinguishes it from conventional SCC and often leads to diagnostic confusion with other clear cell tumors such as renal cell carcinoma metastasis or clear cell melanoma [1]. CCSCC has been documented in both cutaneous and mucosal locations, with the skin and oral cavity being the most commonly affected sites.

The rarity of this variant contributes to limited clinical awareness and challenges in establishing standardized diagnostic and treatment protocols. Histologically, the clear appearance of tumor cells is often due to intracellular glycogen accumulation, which can be demonstrated using periodic acid–Schiff (PAS) staining [2].

Although CCSCC shares many clinical and pathological features with conventional SCC, its biological behavior is not fully understood. Some reports suggest a more aggressive course, while others indicate comparable outcomes. This review aims to consolidate current knowledge and highlight the importance of accurate diagnosis and appropriate management.

Etiology and Risk Factors

The etiology of CCSCC largely parallels that of conventional squamous cell carcinoma. Ultraviolet (UV) radiation is a primary risk factor in cutaneous cases, causing DNA damage and mutagenesis in epidermal cells [3]. Chronic sun exposure is strongly associated with tumor development, particularly in fair-skinned individuals. In mucosal CCSCC, tobacco use and alcohol consumption are significant risk factors, especially in oral and esophageal cases. These carcinogens induce genetic mutations that promote malignant transformation [4]. Human papillomavirus (HPV) infection has also been implicated in certain SCC variants, particularly in the anogenital and oropharyngeal regions.

Additional risk factors include chronic inflammation, immunosuppression, and exposure to environmental carcinogens. Organ transplant recipients and patients with compromised immune systems show a higher incidence of SCC and its variants [5].

Despite these associations, the specific factors contributing to the development of the clear cell phenotype remain unclear. Further research is required to understand the molecular triggers underlying this distinct morphology.

Pathogenesis

The pathogenesis of CCSCC involves molecular mechanisms similar to conventional SCC, including genetic mutations and dysregulation of cellular signaling pathways. A key event is the mutation of tumor suppressor genes such as TP53, leading to impaired DNA repair and uncontrolled cell proliferation [6].

The defining feature of CCSCC is the presence of clear cytoplasm, which is often due to glycogen accumulation. This is confirmed by PAS-positive staining that is diastase-sensitive, indicating glycogen rather than mucin or lipid content [6]. In some cases, hydropic degeneration or lipid accumulation may also contribute.

Alterations in signaling pathways such as EGFR and PI3K/AKT further promote tumor growth and survival. These molecular changes enhance proliferation, inhibit apoptosis, and facilitate tumor progression.

Clinical Features

Clinically, CCSCC presents similarly to conventional SCC, often as a nodular or ulcerated lesion. In cutaneous cases, lesions commonly occur in sun-exposed areas such as the face, neck, and extremities [7].

Patients may present with a rapidly growing mass, ulceration, or bleeding. In oral CCSCC, symptoms include non-healing ulcers, pain, and difficulty in chewing or swallowing. The clinical course may vary depending on tumor location and stage.

Some studies suggest that CCSCC may exhibit more aggressive behavior, including a higher tendency for local invasion and metastasis. However, evidence remains limited due to the rarity of this variant.

Early detection and clinical suspicion are critical for timely diagnosis. Regular screening and biopsy of suspicious lesions are recommended, especially in high-risk individuals.

Differential Diagnosis

Differential diagnosis for clear cell carcinomas depends heavily on the primary site, but generally includes

- Metastatic renal cell carcinoma
- Yolk sac tumor
- Struma ovarii,
- Various clear cell variants of other carcinomas
- (squamous, mucoepidermoid, or myoepithelial) [8]

Histopathological Features

Histopathologically, CCSCC is characterized by nests and sheets of malignant squamous cells with abundant clear cytoplasm. The nuclei are often pleomorphic with prominent nucleoli, and mitotic figures may be present [8]. This clearing is most commonly due to dissolved intracellular glycogen or lipid during tissue processing, leaving behind a vacuolated or empty appearance. Special stains such as periodic acid–Schiff (PAS) may highlight glycogen content, often showing positivity that is diastase-sensitive.

The nuclei of tumor cells may range from small and uniform to pleomorphic and hyperchromatic, depending on the tumor grade. Prominent nucleoli may be visible in higher-grade lesions. Mitotic figures can also be observed, with increased frequency correlating with aggressive behavior.[9]

A key diagnostic feature is the presence of keratinization, which confirms squamous differentiation. However, this may be focal or minimal in some cases, making diagnosis challenging. Special stains such as PAS are used to identify glycogen within the cytoplasm.

Cell borders are usually distinct, and the cytoplasm appears finely vacuolated or granular. In some cases, the cells may exhibit a “hobnail” appearance, particularly in clear cell carcinomas of the ovary or endometrium, where nuclei protrude into glandular lumina.

Additional features may include intracytoplasmic inclusions, hyaline globules, or extracellular mucin, depending on the subtype.

Immunohistochemistry plays a crucial role in differentiating CCSCC from other clear cell tumors. Tumor cells typically express cytokeratins (e.g., CK5/6, p63), supporting squamous origin, while markers for other tumors (e.g., RCC marker, S100) are negative [9].

In summary, the histopathological diagnosis of clear cell carcinoma relies on identifying clear cytoplasm, characteristic architectural patterns, a rich vascular network, and varying degrees of nuclear atypia. These features, combined with clinical and immunohistochemical findings, allow accurate classification and guide management.

Diagnosis

Diagnosis of CCSCC requires a combination of clinical evaluation, histopathology, and immunohistochemistry. Biopsy remains the gold standard for confirming the diagnosis [9].

Histological examination reveals clear cell morphology, but additional tests are necessary to determine the nature of the cytoplasmic clearing. PAS staining is commonly used to detect glycogen, while mucicarmine staining helps exclude mucin-producing tumors.

Immunohistochemical markers such as p63, p40, and cytokeratins confirm squamous differentiation. Negative staining for markers like S100 and HMB-45 helps exclude melanoma.

Radiological imaging, including CT and MRI, may be used to assess tumor extent and metastasis. Accurate diagnosis is crucial for appropriate management and prognosis.[9]

Treatment and Management

Management of CCSCC generally follows the principles of conventional SCC treatment. Surgical excision with clear margins is the primary treatment modality for localized tumors [10]. Surgical management is the cornerstone for most localized tumors. Complete surgical excision with clear margins is the primary goal. For example, in renal clear cell carcinoma, partial or radical nephrectomy is performed depending on tumor size and extent. In gynecologic sites such as ovary or endometrium, staging surgery (including hysterectomy, salpingo-oophorectomy, and lymph node assessment) is typically done.[10]

Radiotherapy may be used in selected cases, particularly for tumors that are not fully resectable, for local control, or for palliation of symptoms like pain or bleeding. Radiotherapy may be used as an adjunct or alternative in inoperable cases. Advanced or metastatic CCSCC may require systemic therapies, including chemotherapy and targeted therapy.

Recent advances in immunotherapy, particularly immune checkpoint inhibitors, have shown promising results in SCC and may be applicable to CCSCC.

A major advance has been the use of targeted therapy, especially in renal clear cell carcinoma. These therapies inhibit pathways involved in tumor growth and angiogenesis, such as VEGF and mTOR pathways. Drugs like tyrosine kinase inhibitors (TKIs) are commonly used in advanced disease. [10]

Immunotherapy has become a key component, particularly for advanced renal clear cell carcinoma. Immune checkpoint inhibitors (such as PD-1/PD-L1 inhibitors) enhance the body's immune response against tumor cells and are now standard in many treatment protocols, either alone or in combination with targeted agents.

Regular follow-up is essential due to the potential for recurrence and metastasis. Preventive measures, including sun protection and lifestyle modifications, are also important in long-term management.

Conclusion

Clear Cell Variant of Squamous Cell Carcinoma is a rare and diagnostically challenging entity. Its unique histological features require careful evaluation to differentiate it from other clear cell tumors.

Although its pathogenesis and biological behavior are not fully understood, current evidence suggests similarities with conventional SCC. Accurate diagnosis using histopathology and immunohistochemistry is essential for appropriate treatment.

Further research is needed to better understand its molecular basis and clinical behavior. Increased awareness among clinicians and pathologists will improve diagnostic accuracy and patient outcomes.

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