Short Commentary

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Unveiling the unexplored: shedding light on a novel aspect of colorectal carcinoma

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Abstract: Colorectal cancer (CRC) remains a prevalent malignancy worldwide, with a significant burden on public health despite advancements in screening and treatment modalities. While the majority of CRC cases are histologically classified as adenocarcinomas not otherwise specified (NOS), there exists a subset characterized by clear cell features or enteroblastic differentiation, which pose diagnostic and therapeutic challenges. This commentary explores the clinical and pathological aspects of these rare colorectal neoplasms, highlighting their distinct characteristics and aggressive behavior. Despite their rarity, clear cell adenocarcinomas or those with enteroblastic differentiation represent a notable proportion of CRC cases and are associated with adverse prognostic implications, including higher TNM stage and poorer survival outcomes. We advocate for a clearer recognition and classification of these entities within the framework of colorectal carcinoma, analogous to existing categorizations in other gastrointestinal malignancies, to facilitate optimal management strategies and further elucidate their underlying biology.

Keywords: colorectal adenocarcinoma; clear cell; enteroblastic

Introduction

Colorectal cancer (CRC) is one of the most common cancers in the world, with an estimated 1.9 million new cases and a death rate of roughly 930,000 persons per year. Projections suggest a potential rise in these numbers over the next two decades [1], despite recent improvements and progress in colorectal carcinoma screening [2].

CRC arises from a complex interplay of genetic, environmental, and lifestyle factors. Risk factors include age, family history of colorectal cancer, inflammatory bowel disease, hereditary syndromes such as Lynch syndrome and familial adenomatous polyposis. Dietary factors such as high intake of red and processed meats, low intake of fibers, and obesity are also implicated [3]. Molecular alterations in both oncogenes and tumor suppressor genes, including KRAS, APC, BRAF, TP53, PIK3CA, and SMAD4, as well as microsatellite instability (MSI), are known to play significant roles in the pathogenesis of colorectal cancer [4].

The therapy for colorectal carcinoma relies on a combination of surgical interventions, chemotherapy, radiotherapy, and targeted therapies, tailored to the disease stage and patient features. Surgical treatment forms the cornerstone, aiming to excise the tumor and affected surrounding tissues, often followed by adjuvant therapy to prevent recurrence. In cases of locally advanced or metastatic tumors, chemotherapy and radiotherapy may be employed pre- or post-operatively to downsize the tumor, enhance surgical efficacy, or control advanced disease. Targeted therapies, such as monoclonal antibodies targeting EGFR or VEGF receptors, have become pivotal in treating metastatic colorectal carcinoma, significantly improving patient prognosis [5]. Additionally, immunotherapy is emerging as a promising therapeutic option for patients with advanced stage tumors [6].

Colorectal cancer from a pathological perspective

Colorectal adenocarcinoma is the most common histotype of colorectal cancer, representing approximately 90% of all cases [7]. Histologically, these tumors exhibit a spectrum of features ranging from well-differentiated to poorly differentiated adenocarcinomas. Well-differentiated adenocarcinomas typically retain glandular architecture and mucin production. In contrast, poorly differentiated adenocarcinomas lack glandular differentiation and exhibit high-grade cytological features such as nuclear pleomorphism and

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increased mitotic activity. The pathological staging of colorectal adenocarcinoma is crucial for determining prognosis and guiding treatment decisions. In addition, histological subtypes could impact on prognosis. Indeed, the latest “WHO classification of digestive system tumors” classifies several histological subtypes of colorectal adenocarcinoma, having signet-ring cell adenocarcinoma, micropapillary adenocarcinoma, and carcinomas with sarcomatoid components more aggressive biological behavior and associated with a less favorable prognosis [7].

Colorectal adenocarcinoma: are we missing something?

Within the spectrum of colorectal adenocarcinomas categorized as NOS, a subset with clear cell features has been described that demonstrates distinct morphological, biological, and molecular features. Since Hellstrom and Fisher’s initial description of adenocarcinoma with clear cell features in 1964 [8], numerous authors have explored these infrequent morphological features, frequently employing ambiguous terminology for their designation. Some authors have hypothesized that the clear cell appearance of neoplastic cell cytoplasms could resemble those of fetal intestinal epithelium, potentially expressing the oncofetal markers Glypican 3, SALL4, and Alpha-fetoprotein (AFP) through immunohistochemical staining [9, 10]. These morphological and immunophenotypic features have led many authors to refer to this class of neoplasms as colorectal adenocarcinoma with enteroblastic differentiation (CAED), similar to gastric adenocarcinoma with enteroblastic differentiation (GAE) [11]. Surprisingly, the “WHO classification of tumors of the digestive tract” recognizes this latter entity by grouping it with the hepatoid subtype of gastric adenocarcinoma [7]; conversely, this does not occur regarding adenocarcinoma of the colon. In the literature, cases of clear cell adenocarcinoma or those with enteroblastic differentiation in the colon are primarily reported as individual case reports. The largest case series reported, conducted on over 900 cases of colorectal adenocarcinoma, highlights how adenocarcinomas with clear cell features or enteroblastic differentiation represent up to 4% of cases, with a significant presence of lymphovascular invasion, lymph node metastasis, and higher TNM stage at diagnosis. Adenocarcinomas with clear cell features or enteroblastic differentiation exhibited a worse prognosis, with statistically significant differences observed in both overall and progression-free survival rates [12].

Conclusions

This brief commentary underscores the imperative of recognizing and comprehensively understanding the existence of clear cell adenocarcinomas or those demonstrating enteroblastic differentiation within the spectrum of colorectal neoplasms. Despite their infrequency, these tumors exhibit notably aggressive clinical behavior, warranting meticulous attention and further elucidation. The authors emphasize the need to recognize the existence of this histotype due to the high and rising incidence of colorectal adenocarcinoma. This aggressive variant is often underestimated, despite its significant impact on patient prognosis. Given that similar histotypes have already been codified in other gastrointestinal malignancies, the authors advocate for a refined classification system. This system would mitigate confusion and ensure that these aggressive tumors receive appropriate attention and management, reflecting their true clinical significance.

Weaknesses lie in the scarce incidence of these clear cell features or enteroblastic differentiation, compounded by potential underrecognition and underestimation. Pathologists, particularly those not specialized in gastrointestinal pathology, may inadvertently overlook these entities, contributing to their underestimation. Furthermore, the absence of standardized diagnostic criteria and terminology exacerbates the challenge of identifying and characterizing these tumors accurately.

The existing literature, although sparse, highlights the significant and aggressive nature of clear cell adenocarcinomas. These tumors frequently present at more advanced stages and are associated with a higher incidence of adverse prognostic factors, including lymphovascular invasion, perineural invasion, lymph node metastasis, and elevated TNM stages at the time of diagnosis. Recognizing these unique colorectal cancer subtypes poses several challenges but also offers significant opportunities. Firstly, bringing these subtypes to light allows for the collection of comprehensive data, facilitating in-depth studies of their biological characteristics. This understanding can lead to improved prognostic stratification for patients with colorectal adenocarcinoma, ensuring that those with more aggressive subtypes are identified and managed appropriately. Additionally, in an era increasingly focused on precision medicine and tailored therapies, characterizing these subtypes paves the way for developing specific therapeutic strategies that cater to the individual patient. This approach not only enhances treatment efficacy but also improves overall patient outcomes, making it imperative to
address and integrate these subtypes into routine clinical practice.

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**References**


