Understanding gastric adenosquamous cell carcinoma: Insights from immunoprofiling

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Gastric adenosquamous cell carcinoma (GASC), like other adenosquamous cell carcinomas of the digestive system, is a rare histological subtype with aggressive tumor behavior.[1] Recent literature has focused on characterizing the clinicopathological features and distinct clinical outcomes compared to its adenocarcinoma counterpart. While some studies have reported the lower third of the stomach as the most common site for adenosquamous cell carcinoma,[2,3] larger registry database studies have reported a higher frequency in the gastric cardia (upper third).[4,5] Poor differentiation is a common tendency,[4–6] and the presence of a squamous component appears to contribute to a poor prognosis.[7]

In the study titled "Immunoprofile of adenosquamous carcinoma in gastric cancer," Wu et al[8] investigated the clinical features, treatment outcomes, and immunoprofile of GASC to determine the optimal treatment modality for these patients. The authors retrospectively reviewed patients with GASC from a single institute and analyzed their clinical data and tumor samples. The study found that the median tumor size in stage III GASC patients was 6.8 cm, and all of these patients underwent radical gastrectomy followed by adjuvant therapy. The median progression-free survival (PFS) and overall survival (OS) for stage III GASC patients were 6.0 and 11.5 months, respectively. Two patients with stage IV GASC received frontline immunotherapy, with a median PFS and OS of 9.0 and 12.5 months, respectively. Immunoprofiling of the GASC samples revealed that 25% of the samples had deficient mismatch repair (dMMR) protein, 75% had a combined positive score (CPS) of ≥1, and 33.3% had a CPS of ≥10. The study also found that programmed death-ligand 1 expression of ≥5% was significantly associated with superior OS. One stage IV patient with CPS ≥10 and dMMR proteins received nivolumab monotherapy as frontline treatment, resulting in a PFS of 14 months. The study suggests that patients with GASC are more likely to exhibit positive results for CPS and dMMR. It highlights the importance of examining biomarkers and considering immunotherapy as frontline systemic treatment for GASC.[8]

The molecular pathogenesis of GASC is poorly understood. In 2000, Woo et al[9] studied microsatellite instability (MSI) caused by defective DNA mismatch repair (MMR) in gastric carcinomas with squamous differentiation. Among the 17 cases, two (12%) demonstrated high-level MSI (MSI-H) at the examined loci. These tumors also exhibited frame-shift mutations at mononucleotide repeats in specific genes targeted by MSI, including *TGFBR2*, *IGF2R*, *BAX*, and *MSH6*. Interestingly, mutations within the *E2F4* gene were found only in the squamous cell carcinoma portions of the tumors, not in the adenocarcinomatous portions, suggesting the possibility that MSI and the associated mutations may play a role in the squamous transformation of gastric adenocarcinoma.[9] Nevertheless, due to the rarity of this histological subtype, more studies are needed to delineate the role of MSI in GASC.

Overall, Wu et al[8] provide valuable insights into the clinical characteristics, treatment outcomes, and immunoprofile of GASC. It emphasizes the potential role of immunotherapy in the management of GASC patients and suggests the need for further research in this area.

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