Editorial

Combined hepatocellular carcinoma-cholangiocarcinoma with sarcomatoid features: new insights into a rare and aggressive tumor

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The rare entity of combined hepatocellular carcinoma-cholangiocarcinoma (HCC-CC) was first described in 1949 (1), and accounts for 0.4% to 14.2% of primary liver cancers (2-4). Initially thought to be coexisting foci of HCC and CC, either as distinct components or with a transition region between them, more recent studies have characterized HCC-CC as a tumor exhibiting both hepatocytic and cholangiocytic differentiation (5,6). The origin of these tumors is believed to be linked to hepatic progenitor cells, as they exhibit characteristics of stem cells (7-10). Risk factors commonly associated with HCC-CC include viral infection and cirrhosis, known risk factors for HCC (8,11,12).

Advances in diagnostic tools have led to the identification of increasingly diverse features in HCC-CC cases. However, most cases are initially misdiagnosed and treated as metastatic carcinoma, HCC, or intrahepatic cholangiocarcinoma (ICC) (9,12). Given its heterogeneity, the gold standard for diagnosis remains the analysis of operative specimens, as biopsies and fine-needle aspirations (FNAs) yield insufficient tissue for definitive diagnosis, with accuracy barely reaching 12% (12). Long-term outcomes appear worse than for HCC but slightly better than for isolated ICC, with national studies reporting a median overall survival (OS) of 9 months and a 5-year OS of 17.1% (13-16). Surgical resection improves survival, though recurrence rates exceed 50% at 5 years (13,16). Identified prognostic factors include tumor size, satellite nodules, lymph node involvement, multifocality, vascular invasion, carbohydrate antigen 19-9 (CA 19-9) levels, capsule formation, and surgical margins (11,17-19).

Sarcomatoid changes are rarely observed in epithelial malignancies like carcinomas and were first described in association with HCC-ICC by Nakajima *et al.* in 1988 (20). The prognostic impact of this feature is controversial, though the presence of sarcomatoid areas is generally associated with aggressive tumor behavior, rapid growth, metastasis, low resectability, and high recurrence rates post-curative surgery (21). The origin of sarcomatoid changes remains debated, with some linking it to prior local liver treatments, such as radiation therapy or transarterial chemoembolization, which may induce necrosis and tissue degeneration (8).

In a recent issue of the *Journal of Gastrointestinal Oncology*,

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Lee *et al.* present an impressive cohort of HCC-CC, 8.8% of whom exhibited sarcomatoid changes (22). This large sample enables statistical evaluation and provides valuable insights into this rare but aggressive disease. Patients with sarcomatoid changes experienced significantly worse OS and disease-free survival (DFS), with multivariate analysis identifying sarcomatoid changes as a poor prognostic factor [hazard ratio (HR) 3.84; 95% confidence interval (CI): 1.63–9.10, P=0.002]. One additional factor that could have been considered in the multivariate analysis is tumor differentiation, as nearly all patients had poorly or undifferentiated tumors. Whether sarcomatoid changes independently affect prognosis beyond tumor differentiation remains an open question. Interestingly, recurrence patterns—whether intrahepatic or extrahepatic—did not significantly differ between patients with and without sarcomatoid changes, likely due to the small sample size, despite both HCC-CC and sarcomatoid subtypes being prone to metastasis. Most patients with sarcomatoid changes did not receive preoperative liver-directed therapy, casting doubt on the theory of mesenchymal features arising from prior treatments and raising questions about its pathogenesis.

The study also prompts reconsideration of whether the presence of sarcomatoid changes should influence adjuvant chemotherapy decisions. There is currently no standard chemotherapy regimen for HCC-CC, and even less data exists regarding sarcomatoid variants. The National Comprehensive Cancer Network (NCCN) guidelines suggest regimens with activity against both components, such as gemcitabine and cisplatin, combined with immune checkpoint inhibitors like durvalumab or pembrolizumab (23). In Lee's cohort, patients with sarcomatoid changes more frequently received adjuvant chemotherapy, primarily sorafenib (55.6%), which remains a first-line treatment for HCC (10). Recent studies, however, suggest that platinum-based regimens may be more effective for HCC-CC, underscoring the need for additional research into modern chemotherapy's impact on survival, particularly in the context of sarcomatoid changes (24).

Regarding surgical management, a critical issue is the low rate of lymph node dissection in these primary hepatic tumors, which hovered around 25%. While lymph node dissection is now recommended for ICC staging in NCCN guidelines (23), its role in HCC remains controversial (25,26). Given the challenge of diagnosing HCC-CC through biopsy and imaging alone, should routine lymphadenectomy be considered for all primary liver cancers to account for the possibility of rare features like sarcomatoid changes? If implemented, what would be the impact on both short- and long-term outcomes?

Rare diseases like HCC-CC with sarcomatoid features are unlikely to be the focus of large clinical trials. A potential solution is to include these cases in broader HCC or ICC trials, allowing for subgroup analyses of their outcomes. By encouraging healthcare providers to report their experiences and results, we can build a more robust body of literature, facilitating evidence-based decision-making for this challenging and poorly understood disease. Expanding our understanding through such collective efforts is critical to improving outcomes for patients with this rare but interesting malignancy.

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