Editorial

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Impact of Microsatellite Instability in Signet-Ring Cell and Mucinous Components in Patients With Colorectal Carcinoma

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See Article on Page 58-65

The disease pathogenesis of colorectal cancer (CRC) is influenced by genetic and epigenetic events that occur with tumor initiation and progression [1]. Diagnostic approaches have evolved from relying exclusively on clinical criteria to incorporating pathologic features such as mucinous and signet-ring cell (SRC) carcinomas, PCR-based microsatellite instability (MSI) testing, and immunohistochemistry for loss of DNA mismatch repair (MMR) component expression [2]. In addition, molecular testing is routinely performed in clinical practice for the selection of patients for targeted biological agents and is advocated for prognostic stratification. Efforts to classify CRC that integrate these molecular features have been developed, and efforts to validate and refine these genetic subtypes to include additional genomic features are ongoing [3].

Recently, new molecular subtypes of biological relevance that were associated with different patient outcomes were identified, and four consensus molecular subtypes (CMSs) with distinguishing characteristics based on many CRC datasets, as well as common features among several independent classification systems, were accepted [4]. These are designated as CMS1 to CMS4. CMS1 (microsatellite instability or MSI, immune) is found in 14% of all patients with CRC and is characterized by MSI, CpG island methylator phenotype (CIMP)-high hypermutation, *BRAF* mutations, increased expressions of genes related to diffuse immune infiltration consisting mainly of TH1 and cytotoxic T cells, activation of pathways to evade the immune system, low somatic copy number alterations and a worse prognosis after relapse. CMS1 includes most MSI carcinomas with overexpression of DNA damage-repair proteins and impaired DNA mismatch repair ability. CMS1 is also frequently found in female patients with right-sided tumors with high histological grade.

In patients with CRC, those with high-MSI cancers (20%) have been shown to have a better overall prognosis than patients with microsatellite stable (MSS) cancers. In patients with MSS cancers, histologic features are more commonly seen that are poorly differentiated, are mucinous, lack dirty necrosis, have increased intense tumor infiltrating lymphocytes (TIL cells), have a circumscribed/expansile growth pattern, and are histologically heterogeneous. For patients with CRC presenting with SRCs, mucinous components (MUCs) and poorly differentiation cells, the tumors are histologically not homogenous, the outcomes are not uniform, molecular features for carcinogenesis are different, and little is known about the prognostic significance of these component [5].

In 1,336 patients with CRC, higher proportions of SRCs and MUCs were both associated with proximal tumor location, MSI-high and CIMP-high cancers, MLH1 promoter hyper-methylation, frequent *BRAF* mutation, and higher LINE-1 methylation level [6]. As to CRC-specific mortality, two cohort studies showed higher mortality in patients with CRC presenting with SRCs (hazard ratio [HR], 1.16; 95% confidence interval [CI], 1.09–1.24), but not MUCs (multivariate HR, 0.99; 95% CI, 0.95–1.04). Those authors 6 also examined the impact of MSI status on the prognosis for patients with CRC presenting with both SRCs and MUCs. They found that the CRC-specific mortality for patients presenting with SRCs did not differ by MSI status. However, in the multivariate analysis, they found that a high-MSI mucinous carcinoma was associated with lower CRC-specific mortality than a MSS mucinous carcinoma. Therefore, they concluded that, compared to the MUC, SRCs were independent of other clinicopathological and tumor-related molecular characteristics.

The author of this study reported that patients with CRC presenting with MUCs, SRCs, and poorly differentiated cells are bet-

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ter stratified by survival when the MSI status of the tumor is considered [7]. However, the analysis had several limitations. Firstly, the size of each pathology group was small. Secondly, the frequencies of patients presenting with MUCs and MSI show geographical variations. Many reported frequencies of MUC are different between Asian (3%–12%) and Western (10%–39%) populations [3]. MSI is also more frequently found in Western patients. In stage III CRC, 11%–21% of Western patients present with MSI whereas 5%–8% of Asian patients do. Thus, a large nationwide study to survey the incidence of MSI in patients with CRC and to identify its impact on prognosis among patients presenting with distinct histologies, such as SRCs or MUCs and high-MSI cancer, is needed.

Theoretically, MMR deficiency causing many somatic mutations may produce 'non-self' immunogenic antigens or neoantigens, as shown by the expression of immune checkpoint ligands PD1, PD-LI, CTLA-4, LAG-3, and IDO., etc. Le et al. [8] actually reported significant responses of cancers with MSI to anti–PD-1 immune checkpoint inhibitors in patients whose cancer had not responded to conventional therapy. This phase II study using pembrolizumab showed that the MMR status of a tumor could be used to predict response to therapy. For patients with MMR-deficient cancer, the immune-related objective response rate and the progression-free survival rate were higher they were for patients without MMR deficiency [8]. This study opened a new window of research associating somatic hypermutation and neoepitope formation with response to immunotherapy.

Gene analysis has proven to be a new approach for judging the potential clinical benefit of immune checkpoint inhibitors [9], such as mutational landscape and mismatch-repair deficiency [10]. Further preclinical and clinical studies are necessary before this idea can be applied in clinical practice.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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