ESHG

COMMENT

Microsatellite instability in gastrointestinal cancers

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European Journal of Human Genetics (2022) 30:996–997; https://doi.org/10.1038/s41431-022-01134-6

INTRODUCTION

Microsatellite instability (MSI) is a genomic alteration in which regions, known as microsatellites, of one to four nucleotide repeats, accumulate mutations corresponding to insertions/deletions of a few bases. MSI is due to a defective mismatch repair (MMR) system.

The MMR system is composed of at least seven proteins, *h-MLH1, h-MLH3, h-MSH2, h-MSH3, h-MSH6*, h-*PMS1*, and h-*PMS2*, which associate with specific partners to form functional heterodimers that recognize base-pair mismatches and small nucleotide insertions/deletions (1–4 base pairs) that occur during DNA replication [1]. Defects in the MMR genes result in failure to correct DNA replication errors, leading to the accumulation of point mutations within microsatellite regions that results in MSI.

Gastrointestinal tumorigenesis is associated with two main genomic instability pathways. One, known as chromosomal instability, is characterized by gross copy number changes with largely unknown causal molecular mechanisms and is believed to occur in at least 60% of cases. The other is the MSI pathway, which induces alterations in the length of repetitive microsatellite sequences [2].

Detected in several human cancers, MSI is particularly common in gastrointestinal (GI) cancers with a frequency of about 15%. As tumors with MSI are associated with specific clinicopathological features, MSI is also used as a diagnostic, therapeutic, and prognostic marker. In this commentary, I will describe the major points above mentioned.

Clinical pathology

The MSI phenotype correlates with specific clinicopathological features of GI tumors. In gastric cancer (GC), MSI is associated with older age at diagnosis, female gender, intestinal histotype tumors, positive family history of GC, and antral tumor location with little invasion of the serosa. Moreover, the MSI phenotype is rarely associated with systemic metastases or with pT3 and pT4 tumors. pN+ lymph node involvement is less frequently identified in patients with the MSI phenotype while vascular and lymphatic invasion are rarely associated with MSI tumors [3]. The overall estimated frequency of MSI in GC is around 15–25% [1].

In colorectal cancer (CRC), MSI associates importantly with right colon tumor location, mucinous histologic sub-type [4], G2-3 tumors, lymphocytic infiltration, and advanced clinical stage IV [5]. The overall estimated frequency of MSI in sporadic CRC is about 10–15%, and in Lynch syndrome around 50% [4–7].

Diagnosis

As a hallmark of hereditary nonpolyposis colorectal cancer, tumor MSI is largely considered a primary feature of individuals with Lynch syndrome. In Lynch syndrome, the most common genetic events causing MMR deficiency are germline mutations in the MMR genes, namely, *h-MLH1*, *h-MSH2*, *h-MSH6*, and *h-PMS2* [1]. However, although a hallmark of Lynch syndrome, MSI is not exclusive to it. MSI has been found in 10–15% of sporadic CRCs. The clinicopathological features and prognosis of sporadic MSI CRCs seem different from those of Lynch syndrome.

In GC, in general the detection of MSI is not associated with Lynch syndrome, however, GC is among the tumors of the Lynch syndrome spectrum. Lynch syndrome is not the cause of all MSI GCs, but certainly, it is a proportion. In hereditary/familial GC panorama, the role of MSI in gastric tumorigenesis is still unclear. Some studies demonstrated that MSI in GC is associated with a positive family history of GC [6], however it does not represent a standard biomarker of hereditary or familial setting GC.

Systemic therapy

Several clinical studies have demonstrated that patients with MSI CRCs do not benefit from treatment with 5-fluorouracil (5-FU) based adjuvant chemotherapies. In general, the 5-FU treatment is used to treat CRC in high-risk stage II cases and as first-line therapy for stages III and IV, but MSI status is not a predictive biomarker of the response to 5-FU in this context [6]. In a recent randomized, open-label, phase 3 study, MSI metastatic CRC patients treated with pembrolizumab monotherapy had a longer progression-free survival, a higher response to treatment, and fewer treatment-related adverse events in comparison to those who were administered chemotherapy as first-line therapy [8].

Although MSI has been consistently proven across many studies to have a positive prognostic value, the evidence suggesting that MSI is a negative predictor of the efficacy of adjuvant or neoadjuvant chemotherapy, remains questionable due to the low number of MSI GC patients described in these studies. At present, MSI status should be used only as a prognostic factor when considering the suitability of a more aggressive surgery as a tailored treatment in GC. Conversely, encouraging results have been reached by the KEYNOTE-012 trial that first demonstrated the efficacy of the anti-PD-1 agent pembrolizumab in PD-L1 positive advanced-metastatic or recurrent GC [9]. Nowadays, MSI or MMR deficiency may be used as biomarker predictive of response to immune checkpoint inhibitors.

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Received: 6 May 2022 Revised: 18 May 2022 Accepted: 9 June 2022
Published online: 21 June 2022

Table 1. Clinicopathological features and potential markers of microsatellite instability in gastric and colorectal cancers.

		pTNM					Invasion			Marker		
Cancer	**Tumor site**	**pT**	**pN**	**pM**	**Grade**	**Histotype**	**Vascular**	**Lymphatic**	**Lymphocytes**	**Diagnostic**	**Therapeutic**	**Prognostic**
Stomach	Antrum	T1-T3	N0	M0	3	Intestinal	Absent	Absent	Absent	No-FGC	No^{PC} - $Yes^{M/RC}$	Yes
Colo-rectum	Right	T3-T4	N +	M0	2-3	Mucinous	Present	Present	Present	Yes-HNPCC	No^{PC} - Yes^{MC}	Yes

PC primary cancer, *MC* metastatic cancer, *M/RC* metastatic/recurrent cancer, *FGC* familial gastric cancer.

Prognosis

Although in different ways, both CRC and GC show an overall favorable prognosis when they are associated with MSI.

MSI phenotype is considered a valid predictive biomarker of good prognosis in advanced gastric tumor. The MSI phenotype correlates with a subset of tumors with similar growth patterns but little propensities to invade serosal layers and spread systemically or via lymph nodes. Considering the locoregional growth of this class of tumors, one could argue for an aggressive surgical approach even in very advanced cases, because survival scores show a high survival rate also in advanced GCs [3].

Berardinelli et al. reported that in CRC, MSI patients had a significantly higher 5-years probability of survival than MSI negative cases. Better survival rates are observed for patients with clinical stage II and III, absence of angiolymphatic and perineural invasions, and no recurrence of disease [5].

CONCLUSION

MSI is caused by genetic or epigenetic inactivation of MMR genes and it is identified with a relatively high frequency in gastric and colorectal tumors. In general, MSI in GI cancers correlates with advanced loco-regional tumor disease. Although clinically and pathologically different in gastric and colorectal tumors, the MSI phenotype represents a validated prognostic biomarker for GI cancers. Patients with an MSI pattern show longer rates of both overall and specific survival with favorable prognosis. In the case of CRC, MSI is possibly diagnostic of Lynch syndrome, but not in cases of familial GC. Finally, MSI should not be used as a predictive biomarker of response to chemotherapy in an adjuvant setting. In a neo-adjuvant setting, the matter remains open. Promising trials demonstrated a possible predictive role only in relation to the response to the administration of pembrolizumab in PD-L1 positive cases of metastatic/recurrent gastric and colorectal tumor (Table 1).

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ACKNOWLEDGEMENTS

The preparation of this study was partially supported by the Italian Ministry of Health with Ricerca Corrente and 5 ×1000 funds.

COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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