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MICROSATELLITE INSTABILITY AS AN EXPERT BIOMARKER IN CANCER DISEASES

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Abstract

The diagnostic and predictive activities of the oncology service are based on a wide range of immunohistochemical and genetic studies with a different spectrum of applications and different levels of efficacy. An analysis of the results obtained are given which outlined the issues of oncopathology of various localization genetic diagnostics efficacy by determining the level of damaged loci with a typical structure – microsatellites onside the genome of tumour cells. The diagnostic importance of microsatellite instability degree was clarified to determine the oncological diseases manifestation prognosis and the risks of malignancy, including metastasis. The author noted the necessity of patient's RER+ status correct interpretation. Based on the results analysis the conclusions were made regarding the value of microsatellite instability genetic marker determination as an additional criterion of oncopathology which allows predicting certain malignant neoplasms clinical manifestation and determining the risks of metastasis of tumours with varying degrees of microsatellite instability.

Key words: microsatellite instability; malignant tumors; colorectal cancer; breast cancer.

The list of methods of oncological pathology diagnosing and its manifestation prediction is constantly extended with a wide range of immunohistochemical and genetic investigations with high potential of efficacy. The necessity for more detailed investigation of cell genome mutagenic potential of both exon-intron and satellite components are of great importance in recent years.

The instability of intron and satellite regions determination which for a long time were considered to be the ballast part of DNA as its non-structural parts is of particular importance now. We have counterarguments to this thesis nowadays although introns and satellites significance still remains not fully understood.

Carcinogenesis itself characterizes by mutations accumulation in genes that control the epithelial cells growth and differentiation which results in their genetic instability. Two independent pathogenetic pathways of genetic instability were established. The first mechanism defined as "*chromosomal instability*" is found in the majority of malignant tumors where it manifested in the form of chromosomal amplifications, transformations, aneuploidy and loss of heterozygosity. Tumors that develop due to the second pathway activation are characterized by a disturbance in mechanism of DNA unpaired pairs repair. This results to cellular genome mutations accumulation with greater rate comparing the same in the normal state. Such an unpaired DNA bases repair inability might be easily determined by DNA microsatellites length. These changes are called "*microsatellite instability*" (MSI) [1, 2].

The mismatch repair system (MMR) is responsible for the recognition and removal of mismatched bases resulting from errors in DNA replication.

At the first stage, the MSH protein complex recognizes mismatched bases which initiate its attachment to MLH_1/PMS_2 and MLH_1/MLH_3 proteins. These proteins, in turn, involve both exo- and endonucleases into the error-removal process which remove the altered DNA region. Replication factors are then recruited to restore the DNA chain nucleotide sequence. Along with errors in replication process, this repair system eliminates the effects of DNA exogenous chemical damage, for instance, in response to platinum drugs influence. Cells with this repair system deficiency demonstrate higher frequency of mutations compared to normal cells. MCH molecule is biomarker of the described genetic disorders of the repair system. Six genes are known to be responsible for DNA unpaired bases repair system: MSH_2, MLH_1, PMS_2, MSH_3, MSH_6 and MLH_3 [3].

Thus, abnormalities in DNA mismatch repair system lead to the formation of frameshift mutations characterized by early stop-codon occurrence and gene inactivation [4]. Despite the different mechanisms of genome damage in both MCI and microsatellite stability (MSS) tumors, the same genes and signaling pathways are disrupted as a result [5, 6]

Microsatellite sequence instability is a sequence of genome mutations increased frequency. The microsatellites (DNA region consisting of short repeats, from 1 to 6 nucleotide pairs long, scattered throughout the genome) peculiarity is a high level of individual variation. Changes in the microsatellite sequences of tumor cells, accompanied by deletions or insertions of one or more repeats, have been called as "*microsatellite instability*" (MI).

Analysis of highly polymorphic microsatellite loci not only provides information about MSN, but also allows to detect normal alleles deletion of suppressor genes in tumour cells. A change in microsatellite sequences length as a result of several nucleotides both deletion or insertion is expressed in additional microsatellite alleles appearance inside the tumour cells that differ in length from alleles in normal tissues of the same patient. If a high level of microsatellite instability (MSI-H) is determined in the studied tumour, i.e. more than 30% of microsatellites are damaged, then the tumour has a RER+ (replication error) positive phenotype. That means that hundreds and thousands of mutations in microsatellite sequences have accumulated in DNA of its cells. Definition of "*low level of microsatellite instability*" (MSI-L) was proposed to use in case of change in the length of less than 30% of markers [7].

MSI was mentioned above to be the genetic biomarker of reparative system described disorders. Microsatellite DNA repeats are polymorphic DNA sequences, 15 base pairs long, which can be repeated up to 1530 times and are distributed throughout the genome. The length of such repeats can vary between tumor cells and normal cells in the same patient [8].

Polymerase chain reaction and immunohistochemistry are most often used currently for MSN level determination.

Polymerase chain reaction amplifies microsatellite repeats in DNA, and by comparing the length of microsatellite repeats between tumour and normal cells, the level of genome instability can be determined. The reference model of 510 microsatellites used allows us to distinguish 3 variants of MSI: MSI-H - high level - 30% of markers are unstable; MSI-L - 10-30% of markers are unstable; MSS - microsatellite stability. Immunohistochemistry ca be an alternative method - the level of proteins of DNA unpaired base repair system is determined.

MSI is diagnosed in case of this repair system proteins deficiency [9].

The aim of the work is to evaluate the role of microsatellite instability genetic marker for the diagnosis of oncopathology of various localizations and to determine the parameters of malignancy of tumours with different levels of microsatellite instability.

Material and methods

We analyzed publications of specialists who performed studies of genetic structure for MSI presence among patients undergoing treatment [10-14].

According to Scientific-Research Institute of Oncology (Kyiv, Ukraine) data of 672 hospital charts were analyzed. Patients underwent molecular genetic examination - a test for molecular instability which involves the use of 3 mononucleotide markers (BAT26, BAT25 and BAT40). A main group of 16 patients was formed - group No 1. Selection criteria were the following: age up to 50 years, presence of NOTSS associated diseases.

We used also the archival pathomorphological sections obtained from 71 patients with bilateral breast cancer (group No 2) [11-13]. The collection of the first tumours corresponded to 1962-1993 years, the median age of women at the time of disease was equal to 50.2 years (age ranges from 27 till 85 years). The collection of contralateral tumours corresponded to 1985-1996, the median age at the time of second tumour was equal to 57.5 years (age ranges from 37 till 87 years). 11 pairs of BRCs were synchronous (the time interval between the tumours occurrence was no longer than 1 year), 60 cases were metachronous tumours.

The control group was consisted by 52 cases of breast cancer diagnosed in the period from 1995 till 1999 years, the median age of the patients was equal to 56.0 years.

A relatively high MSI rate was observed in esophageal cancer in a study provided by Y. Kagawa et al. [14]. The authors studied 41 cases of esophageal cancer and 44 cases of esophageal dysplasia using seven microsatellite markers (group 3).

Results

The test for MSI was positive in 63% of cases (in 10 of 16 patients studied) in patients with colorectal cancer (group No1). 2-3 markers were involved in 43% (7 tumours) at the same time.

A standard panel of microsatellite markers allowed to detect RER+ status in 10% (6-60) of contralateral tumours obtained from patients with metachronous BRMC (group No 2). Important that similar phenotype failed to be detected in any of the first 50 tumours available for study. Analysis of 11 pairs of synchronous BRMCs established microsatellite instability in 1 of 22 carcinomas. The RER+ phenomenon was not registered in the control group, consisting of 52 monolateral BRMCs.

MSI was present in 42% of patients of group No 3 with esophageal cancer (in 17 cases out of 41) and in 59% in patients with esophageal dysplasias (in 26 cases). Moreover, MSI was recorded in 80.1% (in 21 cases) of dysplasias with a mutator phenotype and in 19.9% (in 5 cases) of dysplasias with a non-mutator phenotype.

Discussion

Lynch syndrome is a hereditary disease caused by inactivating germline mutations presence in genes encoding proteins of DNA mismatch repair system [15]. It is inherited in an autosomal dominant manner, with a 23-75% risk of colorectal cancer development [16].

Mutations in 5 repair genes have been described. Additionally to characteristic features of microsatellite tumours – proximal localization, mucinous variant and low grade differentiation - patients with Lynch syndrome often have a primary multiple lesion pattern including tumours of the colon, endometrium, stomach, ovaries, urinary tract, small intestine and other organs, but without an increased incidence of lung, breast or prostate cancer [17].

The MSI prognostic role in colorectal cancer (CRC) is determined as follows: MSN is detected in 22% of cases in stage II CRC, 12% - in stage III CRS and 2% in stage IV CRC [18].

According to data obtained, the test for MSI is positive in 63% of cases. These signs may be useful as diagnostic markers although this phenotype is not confirmed in all studies. In addition, tumours with high levels of MSN and tumours with MSS have different prognosis of disease manifestation and, possibly, have different sensitivity to chemotherapy [19, 20].

High MSN levels in the majority of retrospective studies are associated with better survival after CRC. These findings were confirmed by a meta-analysis of 32 studies demonstrated MSN prognostic value levels in 7642 patients [21].

MSI reflects a defect in DNA base mismatch repair and is not specific to colon tumours as previously thought. Recent studies have identified several tumours with RER+ phenotype in patients with bilateral breast cancer. The studies [11-13] were aimed to further analyze this unexpected phenomenon. MSN testing was positive in 4.5% (1 case out of 22) of synchronous CRC and in 10% (6 cases out of 60) of metachronous bilateral breast cancer. The data presented suggest that contralateral metachronous breast tumours certain proportion development is associated with side effects of the first neoplasm treatment.

MSI test was positive in 42% of esophageal cancer cases and in 59% of esophageal dysplasia cases [14]. Tumours with microsatellite stability had a higher incidence of recurrence and metastases to regional lymph nodes. These tumors had a worse prognosis compared with microsatellite unstable RP. Although the unclear MSI significance in esophageal cancer, the authors suggested that MSI occurs at an early stage of carcinogenesis [14].

Conclusions.

Thus, the genetic marker of microsatellite instability is one of the important additional criteria in oncopathology, which makes it possible to predict the clinical course of some malignant neoplasms and determine the risks of metastasis of tumours with varying degrees of microsatellite instability.

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Data Availability Statement

The data presented in this study are available on request from the author.