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MICROSATELLITE INSTABILITY : CORELATION WITH COLORECTAL CANCER

Tanya Tripathi, A.N. Srivastava, Sharique Ahmad

Department of Pathology

Era's Lucknow Medical College & Hospital, Sarfarazganj Lucknow, U.P., India-226003

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Address for correspondence
Dr. Tanya Tripathi
Department of Pathology
Era's Lucknow Medical College & Hospital, Lucknow-226003
Email: tanyatripathi@rediffmail.com
Contact no: +91-9198228640

ABSTRACT

Colorectal cancer ranks as third most commonly found cancers in human and being found both in male and female equally. All over the world these cancers have been a major problem in public health sector. Chromosomal Instability is among the most common form of genomic stability constituting 85 % of all colorectal cancer, defined as the presence of numerical chromosome changes or multiple structural aberrations of chromosomes.A subset of colorectal cancers (10 to 20 %) has been linked to aberrant methylated CpG loci. CpG Island Methylator Phenotype (CIMP) is characteristic of this subset.Determination of Microsatellite Stability Index status in CRC has prognostic and therapeutic implications and also for classification and has become the need of the hour and its detection by various methods and implications in treatment demands much research so as to improve the prognosis of all types of colorectal cancers and hence provide a path for therapy.

KEYWORDS: MSI, Colorectal cancer, Chromosomal instability.

INTRODUCTION

Colorectal cancer ranks as third most commonly found cancers in human and being found both in male and female equally.All over the world these cancers have been a major problem in public health sector(1). Out of all the patients around 25 % constitutepatients with positive family history for the same cancer and rest 75% are sporadic cancers with no inherited disorders linking it with some sort of environmental interference(2).Inherited mutations contribute to only 6% of patients while rest cases are attributed to epigenetic and genetic alterations of genome(3,4).

Molecular Changes In Colorectal Cancer

- Chromosomal Instability (CIN)
- Microsatellite Instability(MSI)
- CpG island Methylator phenotype(CIMP)

One of the basic aspects of colorectal canceris incorporation of acquired inherited and epigenetic changes which bring forth changes in the normal epithelium of colon into invasive adenocarcinomas. Fearson and Vogelstein proposed the classical tumour progression model showing formation of benign neoplasm which promotes to histologically advanced neoplasm to invasive adenocarcinoma (5). The model showed only tubular and tubulovillous adenomas had the propensity to become full-fledged carcinoma but it was later found that sessile serrated adenomas/polyp too had malignant potential (6, 7). These serrated poly are related to CpG Island Methylator Phenotype (CIMP) and suggest an alternate pathway for malignancy. On the other hand tubular adenoma shows presence of chromosomal instability (CIN) characterised by aneuploidy and alteration in large portions of chromosome producing a state of genomic instability.

Chromosomal Instability (CIN)

It is among the most common form of genomic stabilityconstituting 85 % of all colorectal cancers (8). It can be defined as the presence of numerical chromosome changes or multiple structural aberrations of chromosomes. It has been proposed that oncogene stress induced genomic instability, telomere erosion, and DNA hypomethylation have a role in occurrence of genomic instability though due to scarcity of validated methods to detect this instability it is difficult to compare studies and correlate it clinically(10,11)). They can be detected by various methods including DNA flow cytometry, comparative genomic hybridization, whole exon sequencing, and high-density SNP arrays.(8,9)

CpG Island Methylator Phenotype (CIMP)

A subset of CRC (10 to 20 %) has been linked to aberrant methylated CpG loci. This class of colorectal cancers (CRCs) has been characterized as having a CpG Island Methylator Phenotype (CIMP) and was first described by Toyota et al in 1999 (12). Mechanism

giving rise to CIMP CRCs is unknown but overexpression of the DNA methyltransferases DNMT3B or DNMT1 has been shown to correlate with CIMP in some studies (8). Mutations in genes involved in chromatin remodelling like CHD8 may mediate CIMP. Another stimulus which is environmental exposure (eg tobacco) and IDH1 and TET mutations. These mutations are also seen in gliomas and leukemia but rarely seen in CRC (13, 14).Few researches reveal subclasses of CIMP, comprising of CIMP-low (<2/5 markers), and CIMP-high (>3/5 markers) or CIMP1 and CIMP2, depending on unsupervised cluster analysis result of a panel of methylation markers(15).Even though there are different methods and criteria suggested to classify CIMP still a universal approach which is being accepted is that there are truly unique CIMP subclasses, which likely arise from different polyp types. For example some studies have suggested with evidence that existence of a CIMP subclass derived from traditional serrated adenomas that is CIMP-low, with MSS and carries mutant KRAS . Another CIMP subclass derived from sessile serrated polyps that is MSI-H and carries mutant BRAF is also reported(16).

Various retrospective studies have proved that CIMP will finally be a good prognostic marker and possibly predictive marker for CRC, but the data is inconclusive at this time to recommend its clinical use (15,17).

Types Of Colorectal Cancer And Their Genetic Basis

Sporadic CRC

Being the most common type and constituting 75% of cases these type of CRC do not show apparently any genetic inheritance. It is most common in elderly and have link to environmental, dietary, and aging factors (18). MSI-H sporadic cancers are most commonly caused by alteration of MLH1 gene through the process of somatic promoterhyper methylation (19).

Familial type of CRC

Usually these are sporadic but its seen individual with history of CRC in first degree relative have 2 to 3 fold increase in incidence of CRC(20).

Hereditary Type Of Crc

Familial Adenomatous Polyposis

Familial Adenomatous Polyposis is a common autosomaldominant disease showing mutation of APC gene located on chromosome 5q21. APC protein

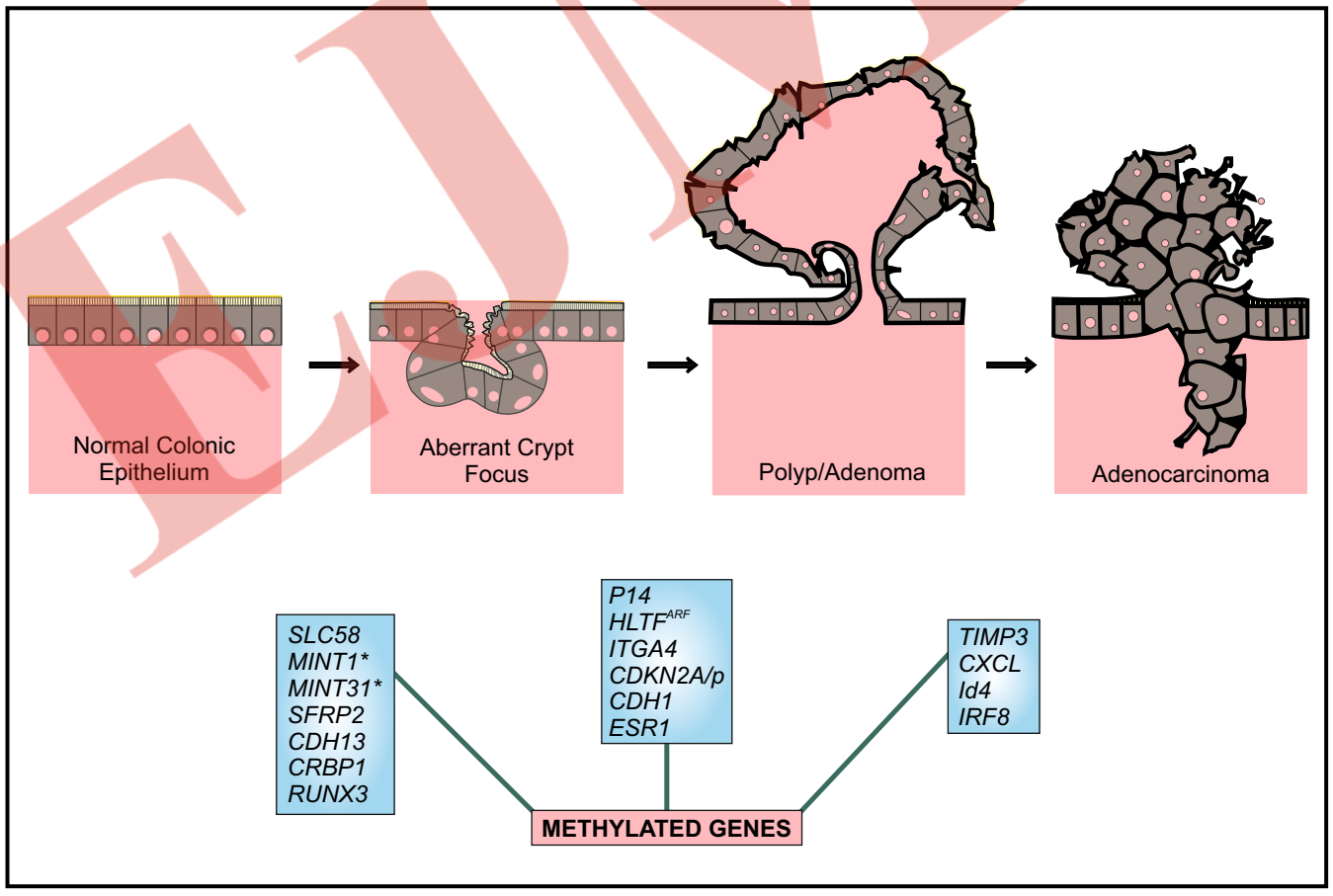

Fig 1: Conversion of Normal Colonic Epithelium into Adenocarcinoma

is produced by the APC gene(a tumour suppressor gene). It is a multifunction protein which is responsible for growth of cells and also acts as check on tumour development. This protein regulates β-catenin by degrading it, which in turn plays a major role in cell communication, Wnt signalling pathway, and growth by acting as a transcription factor for proliferation genes. When this APC gene undergoes mutationleading to loss of APC function and result in an accumulation of β-catenin. FAP is caused by many different mutations (e.g. insertions, deletions, nonsense mutations) of the APC gene (21). Cancerdevelops with occurrence of mutations like K-RAS, DCC, P53, COX-2, BCL-2 (22). The mean age to develop FAP is 35 years and if not diagnosed and treated, there is increase in chances of development of colorectalcancer (23).

MUTYH-associated polyposis (MAP)

This comprises of one of the hereditary polyposis syndromes being autosomal recessive in nature. The main reason is a biallelicgermline mutation in MUTYH gene on chromosome 1p34.1. MYH glycosylaseis an enzyme coded by MUTYH gene and is necessary for DNA repair system called Base Excision Repair (BER). The MAP disease usually has less number of polyps than FAP and is phenotypically similar to attenuated FAP. The usual age of occurrence of MAP is between 40 to 60 years and has 80 % risk of developing CRC (24).

Peutz-Jeghers syndrome (PJS)

Being a rare autosomal dominant disorder ,this syndrome shows hallmark existence of numerous benign hamartomatous polyps including the gastrointestinal tract, most commonly involving the small intestine. The number of polyps in PJS is less than MAP syndrome and they exists since birth or early age (25). Germ line mutations in the STK11 (serine threonine kinase 11) gene, also called LKB1, a tumour suppressor gene present on chromosome 19p13.3 is the main cause behind this syndrome (26). Conformational change is seen in STK11 protein after mutations leading to decrease in its efficiency to control cell division with loss of kinase activity. These tumours are also seen to be associated with Microsatellite instability, LOH nearby the APC gene, and KRAS mutations (27).

Serrated polyposis syndrome (SPS)

Serrated polyposis syndrome is a relatively rare syndrome also called as the hyperplastic polyposis syndrome with characteric multiple serrated polyps of the colon(28). It involves germline mutations of oncogene-induced senescence pathway genes and is usually sporadic(29). MSI-low or MSS (Microsatellite Stable) are often associated with this syndrome(30).

Lynch syndrome (LS)

Lynch syndrome (LS),is an autosomal dominant disease caused by germline mutations in one of several DNA mismatch repair (MMR) genes, including MSH2 on chromosome 2p16, MLH1 on chromosome 3p21, MSH6 on chromosome 2p16, and PSM2 on chromosome 7p22(31). It is also known as Hereditary non-polyposis colorectal cancer. MSH2 and MLH1 mutations can be held responsible for most of the cases of Lynch syndrome (32). One of the most important role of MMR genes encode proteins is that they help in adequate repair of DNA sequence mismatch and rectify base mismatches, small deletions or insertions(33). Abruption of these genes hinders DNA repair and intiates an alteration in the short-tandem DNA repetitive sequences or microsatellites, resulting in the development of a phenotype known as microsatellite instability which is a hallmark of Lynch syndrome. High-level microsatellite instability is observed in approximately 90 % of LS-associated CRCs (34).

Molecular Basis Of DNA Mismatch Repair System

DNA mismatch repair system (MMR) plays a significant part in editing erroneous insertion, deletion, and base-base mismatches generated during DNA replication and recombination. This repair pathway is highly specific from bacteria to humans and conserves the integrity of the genome(35). Prokaryotes include the proteins MutS and MutL that function as homodimers whereas, in eukaryotes, MSH2, MSH3, and MSH6 are homologs for MutS; MLH1, MLH2, MLH3 are MutL homologs. There are also other homologs for MutL (post-meiotic segregation) named PMS1 and PMS2 which interact as heterodimers (36). When a mismatch is detected in the eukaryotic genome, DNA mismatch repair system functions through a series of steps: MSH2 associates with MSH6 or MSH3 causing the formation of MutSα and MutSβ heterodimers, respectively. MutSα recognizes single base mismatches and small insertion/deletion loops (IDLs), while MutSβ recognizes larger loops. After exchange of adenosine triphosphate (ATP) to adenosine diphosphate (ADP),theMutSα or MutSβ can recruit MutLα, MutLβ or MutLγ heterodimers (if MLH1 couples with PMS2, PMS1 or MLH3, respectively). This MutS-MutL complex gives rise to a sliding clamp around the DNA. The proteins in sliding clamp interact with exonuclease-1 and proliferating cell nuclear antigen (PCNA). This complex excises the daughter strand back to the site of the mismatch. Finally, resynthesize and re-ligation are performed by DNA polymerase and DNA ligase, respectively (37).

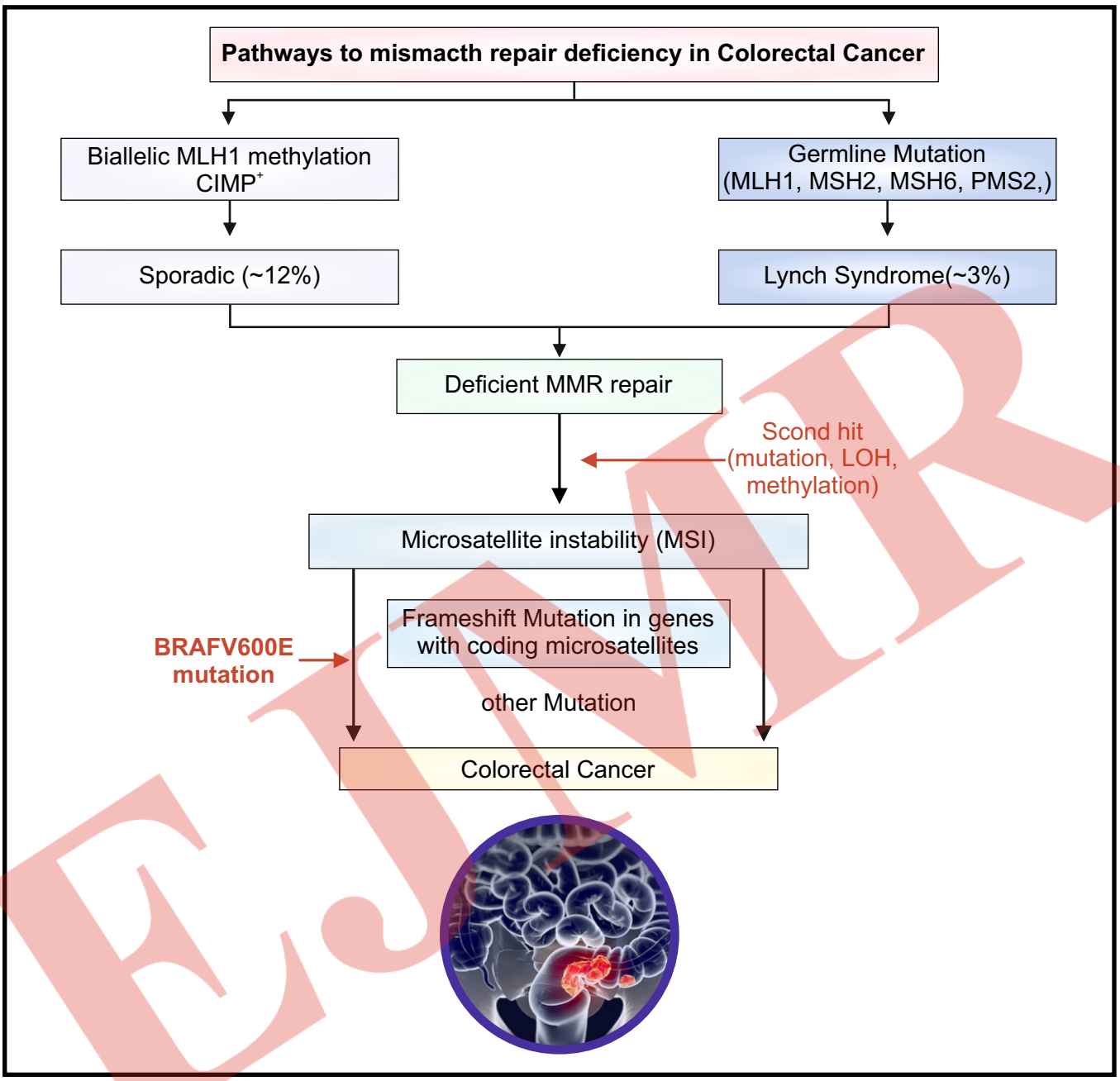

Fig 2: Pathways of Mismatch Repair Deficiency in Colorectal Cancer

Microsatellite Instability (MSI)

Microsatellites, also known as Short Tandem Repeats (STRs) are small (1-6 base pairs) repeating stretches of DNA scattered throughout the entire genome (both in coding and non-coding regions) constituting 3 % of the human genome. Owing to their repeated structure, microsatellites are prone to high mutation rate (38). Microsatellite instability in tumour DNA can be defined as the presence of alternate sized repetitive DNA sequences that are not present in the corresponding germ line DNA. The defect in DNA mismatch repair system gives rise to a molecular phenotype in form of Microsatellite instability (MSI).

Several other cancers like sporadic colon, gastric, sporadic endometrial and the majority of other cancers express MSI (39).Determination of MSI status in CRC has prognostic and therapeutic implications and also for classification (40). MSI has always as always associated with improved prognosis; it proves as a valid reason to change the prospective approach to advanced MSI-high disease. Being highlyimmunogenic, a therapy that strengthens the immune system can have a spectacular effects on unstable tumours. This has encouraged the need to develop tumour vaccines and to

turn MSS tumours into MSI to make them more immunogenic.

Detection of MSI

Two methods

- INDIRECT: By analysis of MMR protein expression by Immunohistochemical (IHC) staining
- DIRECT: By PCRbased amplification of specific microsatellite repeats(common)(41)

IHC Method for Detection

Although not a perfect test for MSI, it tests the expression of mismatch repair proteins in cells. Here antibodies against MMR proteins such as MLH1, MSH2, PMS2 and MSH6 and gives provide information of the MMR system functionality. IHC analysis with PMS2 and MSH6 antibodies is able to detect most abnormalities in the corresponding encoding genes as well as mutations in MLH1 and MSH2; however, IHC assay with MLH1/MSH2 antibodies can detect a fraction of MLH1 or MSH2 abnormalities but not all of them. Therefore, IHC analysis with MSH6 and PMS2 antibodies has more diagnostic potential than analysis with MLH1 and MSH2 antibodies (42). It's mainly used as a screening test for Lynch Syndrome. Universal MSI/IHC on tumours is increasingly performed throughout the world.

PCR-based Method

Here DNA from tumour tissues and normal tissues, a series of primers one of which is fluorescently end labelled (the sense strand or antisense strand of each primer), a sequencer, and appropriate software is needed. The principle of this method is to measure the presence of different lengths of specific microsatellite markers in tumour cells comparing to normal cells (40).

In the first attempt to the diagnosis of MSI in CRC, a consensus conference recommended a panel of microsatellite called Bethesda panel. Markers included three dinucleotide repeats (D5S346, D2S123, and D17S250) and 2 mononucleotide repeats (BAT25 and BAT26). Three distinct MSI phenotypes have been described. If two or more microsatellite markers are mutated, the tumour is considered MSI-high (MSI-H); if only one is mutated, the tumour is defined as MSI-low (MSI-L); and if none of the examined loci demonstrate instability, the tumour will be considered Microsatellite Stable (MSS). This panel was known as the Bethesda panel (43).

A few years later, it was found that mononucleotide markers have a better specificity and sensitivity than dinucleotide repeats (dinucleotide markers have a polymorphic nature) (44) and hence Bethesda guideline criteria were revised by NCI (National Cancer Institute) at the following conference in

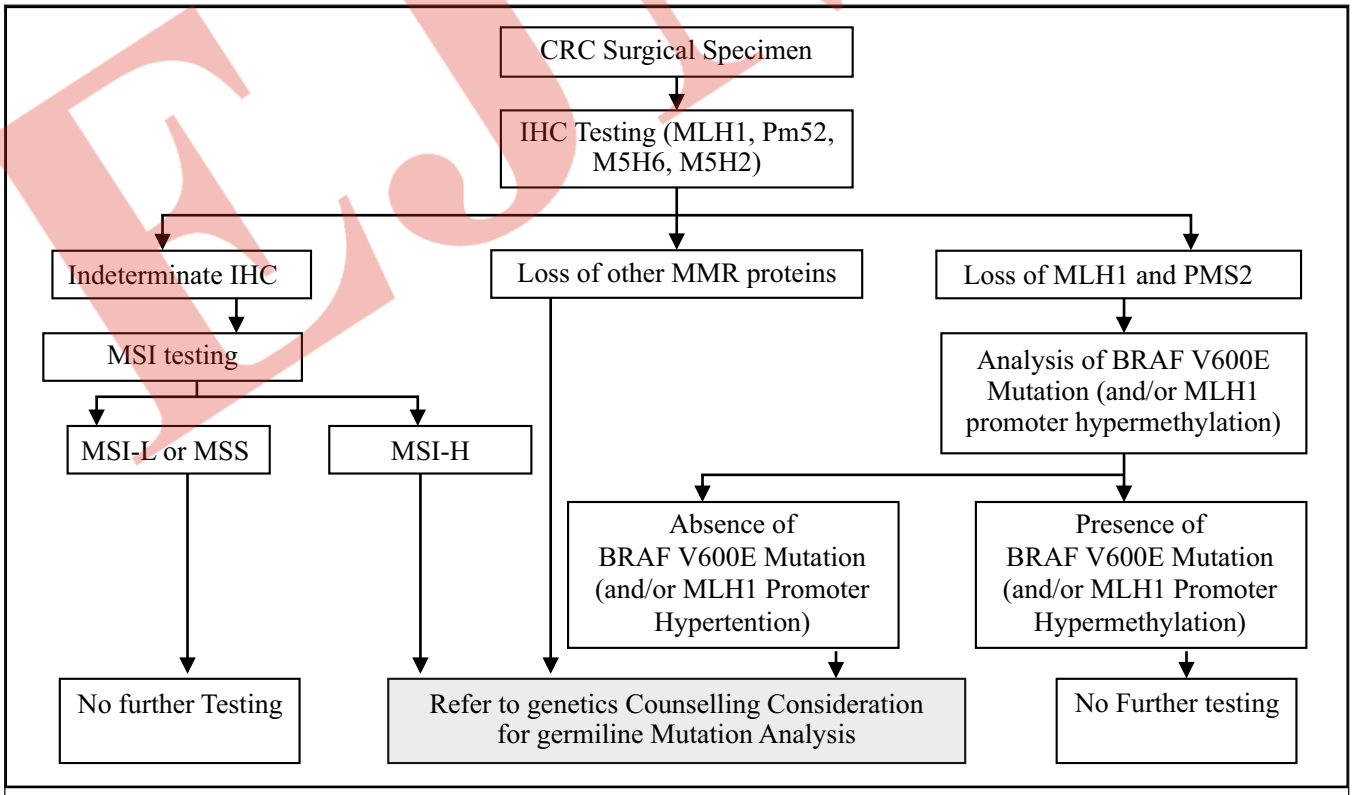

Fig 3: Depicts the Approach to Colorectal Carcinoma with Respect to MSI

2004(45). After that, the uses of panels containing more mononucleotide markers have been increased due to their higher sensitivity and specificity in the diagnosis of MSI in CRCs.

MSI in Treatment and Therapy

Even though the uses of MSI status in predicting the response to adjuvant chemotherapy is controversial still it is understood that colorectal tumours displaying MSI have a better prognosis compared with MSS tumours.

Several studies have shown that individual with dMMr CRCs have more favourable prognosis than those with pMMR (46-50) and more so appears in early stage of tumour (51).

A meta-analysis done out of 32 studies including 7642 patients this stage I-IV CRC showed patients with MSI/dMMR than those with MSS,MSI-L/pMMr tumours among patients that were untreated or treated with 5-fluorouracil (5-FU)-based adjuvant chemotherapy (52).

The chemotherapeutic treatment is effective in some certain patients, but it can cause many adverse effects(53). MSI-H is one of the potential predictive points to the chemotherapeutic treatment efficacy and to the level of adverse effects in a patient; therefore, several clinical trials have been conducted regarding this opinion (54). There are different therapeutic responses in MSI-H CRCs depending on type of adjuvant chemotherapy. Diagnosis is likely Lynch or Methylated when a tumour is to be MSI-high. If IHC is done and the unexpressed protein is MSH2, PMS2 or MSH6 then it is Lynch. Germline testing is indicated. If the unexpressed protein is MLH1 it could be a CIMP tumour with hypermethylation of MLH1 promoter, or Lynch. To tell which is which, BRAF mutation testing or methylation assay on the tumour are helpful. For treatment it is a candidate for immune activation therapy if it is advanced. If not advanced it has a good prognosis and will not respond to 5 FU based therapy.

Recently NCCN in their recent guidelines in 2018 have included MSI testing in their panel specially for patients with genetically related colorectal cancers.

CONCLUSION

Being one of the most prevalent cancers in humans CRC creates a significant public health problem worldwide it is very much necessary to find out ways of diagnosis and treatment of CRC. MSI is significant genetic markers in CRC that can be playing a very helpful role in diagnosis, prognosis, and prediction of chemotherapeutic treatment efficacy.In qualitative studies involve the systematic collection, organization, description and interpretation of textual, verbal or visual data. The particular approach taken determines to a certain extended criteria used for judging the quality ofthe report and treatment of colorectal carcinoma (55). As now is the era of newer and newer molecular techniques hence now more focus lies on tumour specific drug development strategies.

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