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Current Issue in Genetic Colorectal Cancer Syndrome

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Abstract

Introduction: large intestine cancer is that the third common cancer within the world. Regarding 3-5% of the patients area unit carrier of genetic syndrome with high risk of large intestine cancer (CRC) et al malignancy. 20-30% of the patients with new diagnosed large intestine cancer had a case history of large intestine cancer. The foremost common hereditary syndrome is kill Syndrome (HNPCC hereditary non-polyposis large intestine cancer). Alternative syndromes with accumulated variety of polyps embody Familial adenomatous polyposis (FAP), attenuated FAP and MUTYH associated Polyposis (MAP). Genetics: kill syndrome is characterised by a germline mutation at a defective deoxyribonucleic acid couple repair (MMR) genes, with a high level of microsatellite instability. The foremost common genes concerned within the syndrome area unit MLH1, MSH2, MSH6, PMS2 and EpCAM. FAP caused by APC cistron defects and MAP caused by a defect within the MUTYH cistron. Kill syndrome and FAP area unit genetic chromosome dominant, whereas MAP genetic chromosome recessive. Designation is created by genetic investigation, founder mutation and cistron sequencing. Cancer risk: Mutation carrier of the various varieties of the syndromes has accumulated risk of colonic and extra-colonic tumor. The time period CRC risk is calculable to be 50-80% in HNPCC and regarding 100% in FAP. The chance of the malignancy development is betting on mutation and cistron. Clinical setting: Dutch capital criteria and revised Bethesda criteria were developed to spot persons and families with high risk kind kill syndrome. Patients with FAP area unit characterised by thousands of polyps and MAP patients by 10-100 of polyps. Universal screening for kill syndrome: ought to patients with large intestine cancer or endometrial carcinoma bear screening by assay (IHC) or microsatellite instability (MSI) for kill syndrome. Affirmative, many recommendations embody the universal screening for all diagnosed patients below age seventy years. The police work recommendation and treatment with Empirin or cox2 are going to be mentioned. All the higher than points are going to be updated and mentioned throughout the lecture.

Introduction: Colorectal cancer (CRC) is a common malignancy, affecting over 141,000 new patients in the United States and estimated to cause over 49,000 deaths in the year 2011.1 Although the majority of patients with CRC have sporadic disease, up to 30% have a familial component and a potentially definable genetic basis.Over the last twenty years, highly penetrant monogenic germline mutations conferring high lifetime risk of CRC have been identified and account for 5–6% of all CRC cases. These inherited CRC syndromes serve as a paradigm for personalized medicine based on available genomic information

Lynch Syndrome: Lynch syndrome accounts for 3–5% of CRC cases and is caused by a germline mutation in one of four genes associated with the DNA mismatch repair (MMR) system: MLH1, MSH2, MSH6, or PMS2. Aggregation of colorectal and endometrial cancers inherited in an autosomal dominant manner in two large Midwestern kindreds Investigators have subsequently termed this inherited condition along with an expanded constellation of malignancies, and evidence of mismatch repair gene dysfunction, Lynch syndrome.

Clinical Features: Carriers of gene mutations in the MMR genes have a 50–80% lifetime risk of developing CRCAdenomatous polyps are the precursor lesions in the development of CRC and progression of the adenoma to carcinoma sequence in patients with Lynch syndrome is accelerated over a two to three year interval compared to the seven to ten year timeframe in sporadic CRC cases. CRC in Lynch syndrome has an early age of onset, with a mean age of 45 years, and multiple synchronous CRCs are not uncommon. The CRCs have a predilection for the proximal colon and have specific histologic features including poor differentiation, a mucinous component, and an intense Crohns-like lymphocytic reaction. Patients with Lynch syndrome are also at an increased risk for a wide variety of extracolonic malignancies, most notably endometrial cancer. Among women, endometrial cancer is the second most common cancer associated with Lynch syndrome, with an estimated lifetime risk of 40 to 60%. Sebaceous neoplasms of the skin are seen in the Lynch syndrome variant, Muir-Torre syndrome, and Turcot syndrome is associated with brain tumors, including glioblastomas and astrocytomas. The spectrum of Lynch syndrome-associated malignancies also includes cancers of the stomach, small intestine, pancreas, biliary tract, and urothelial carcinoma of the renal pelvis and ureter.

Genetics of Lynch Syndrome: Alterations in the MMR system cause errors in DNA replication to accumulate and not

be repaired, particularly in sequences of DNA known as microsatellites. Microsatellites are short mononucleotide or dinucleotide repeat sequences in which slippage of DNA can occur during replication resulting in either too few or many copies of microsatellite repeat sequences. An intact MMR system corrects these errors when they are not normally rectified by DNA polymerase. The MMR system requires cooperation of genes from the mutS (MSH2, MSH3, MSH6) and mutL (MLH1, MLH3, PMS1, and PMS2) families. A heterodimer complex between MSH2-MSH6 (MutS) recognizes single nucleotide mispairs and binds to the mismatched DNA sequence. A second heterodimer complex between MLH1-PMS2 (MutL) then binds to MutS to remove several bases from the newly synthesized DNA strand. This leads to resynthesis of DNA with the correct base pairing. At microsatellite sequences, insertion-deletion loops of one nucleotide are typically recognized by MSH2-MSH6, but larger insertion-deletion loops are recognized by the heterodimer MSH2-MSH3, followed by binding by MutL, excision, and resynthesis as described previously. The roles of MLH1-PMS1 and MLH1-MLH3 in human MMR function are not entirely clear at this time. For malignancy to occur in an individual with a germline MMR gene mutation, a second copy of the affected MMR gene must be somatically mutated and the altered microsatellites are found in the coding regions of genes involved in tumor initiation and progression.