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The Genetic Discrepancy-Lynch Syndrome

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Abstract

Lynch syndrome is a frequently discerned hereditary cancer syndrome demonstrating the occurrence of colorectal carcinomas in around 80% subjects and endometrial cancers in nearly 60% individuals. Lynch syndrome is accompanied by germ line chromosomal mutation of one of the four Mismatch Repair (MMR) genes, enunciated as MLH1, MSH2, MSH6 or PMS2, which can be discerned with cogent immune histochemical reactions or evaluation of Microsatellite Instability (MSI). Lynch syndrome is generally associated with a cumulative emergence of fewer than ten (<10) colonic adenomatous polyps which can rapidly metamorphose into poorly differentiated, medullary-type carcinoma, mucinous adenocarcinoma, signet ring cells or a Crohn's like reaction. Lynch syndrome requires a segregation from Attenuated Familial Adenomatous Polyposis (AFAP), Turcot's syndrome, MUTYH associated polyposis, MSH3 related susceptibility to polyposis, NTHL1 mutation susceptible polyposis, POLE mutation susceptible colorectal carcinoma, Li-Fraumeni syndrome, hereditary diffuse gastric cancer or hereditary breast and ovarian cancer syndrome. Colonoscopy commencing at 20 years to 25 years, repeated annually or every 2 years to 5 years with colectomy is recommended in colonic cancer or surgically unamenable colonic adenoma.

Keywords

Lynch syndrome; Germline; Adenomatous Polyposis Coli Gene

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Introduction

Lynch syndrome is a frequently cogitated hereditary cancer syndrome, also designated as Hereditary Non Polyposis Colorectal Syndrome (HNPCCS). Colorectal carcinoma is a frequently engendered carcinoma and a common cause of individual mortality. Majority of colorectal carcinomas are sporadic although an estimated 5 to 10% instances appear contingent to inherited cancer syndromes or inherent genetic mutations. Subjects with lynch syndrome enunciate an enhanced emergence of colorectal carcinomas in around 80% subjects and delineate nearly 60% of endometrial cancers [1]. Elevated proportion of associated primary carcinomas such as gastric, ovarian, small bowel, urothelial (ureter and renal pelvis), biliary tract, pancreatic, brain tumors as with glioblastoma and benign conditions as described with sebaceous gland adenoma and keratoacanthoma can be enunciated [1].

Disease Pathogenesis

Lynch syndrome originates from a germline chromosomal mutation of one of the four mismatch repair (MMR) genes as exhibited with MLH1, MSH2, MSH6 and PMS2. Significant chromosomal deletions situated upon a non-mismatch repair gene as cogitated with Epithelial Cellular Adhesion Molecule (EPCAM), curtailing exemplification of MSH2, can also engender lynch syndrome. Mismatch repair genes are cogent in genomic regeneration and correction of nucleotide base pairing occurring during DNA replication. With incorrect base pair matching, suboptimal function of the generated genomic copies is delineated, thereby enhancing the emergence of various carcinomas. Neonates of lynch syndrome demonstrate a congenital functional allele or copy of a particular gene and a singular non-functional allele of a particular gene during inherited mutations [1,2].

Emergence of carcinoma is contingent to genetic mutation acquired within the functional allele. Exceptionally, in neonates displaying an absence of lynch syndrome, carcinoma can occur on account of dual loss of alleles with a consequent absence of somatic mismatch repair protein [2].

Disease Characteristics

Subjects with categorical lynch syndrome depict an enhanced possibility of colonic and extra-colonic carcinomas such as endometrial, ovarian, upper gastrointestinal tract, urothelial, pancreatic and carcinomas of the brain. Screening methodologies for discernment of lynch syndrome are adequately performed upon colorectal and endometrial tumor tissue. Immune histochemical reactions are available for detecting the cogent, four mismatch repair proteins as

cogitated with MLH1, MSH2, MSH6 and PMS2 or evaluation of Microsatellite Instability (MSI) can be adopted [1,2]. Lynch syndrome is inherited as an autosomal dominant condition wherein the first degree relative, parents, siblings and offspring demonstrates a 50% possible occurrence of the syndrome. An estimated 2 to 4% of colorectal carcinomas and approximately 2.5% of endometrial carcinomas are a component of lynch syndrome. Similarly, 1 in 35 instances of colorectal carcinoma and 1 in 50 instances of endometrial carcinomas are attributable to lynch syndrome [2]. Mean age of discernment of colorectal carcinoma is 44 years to 61 years whereas endometrial carcinoma is observed at a mean age of 48 years to 62 years [2].

Clinical Elucidation

Lynch syndrome is generally associated with a cumulative emergence of fewer than ten (<10) adenomatous polyps. Commonly, adenomas depict a villous pattern with moderate to high grade dysplasia and appear below <40 years. Colorectal adenomas and colonic malignancies associated with Lynch syndrome are frequent upon the right colon [3]. Possible emergence of colorectal carcinoma is nearly 52 to 82% wherein mean age of neoplastic discernment is 44 years to 61 years.

Endometrial carcinoma appears in around 25 to 60% female subjects with a mean age of tumor diagnosis at 48 years to 62 years. Gastric carcinoma occurs in roughly 6 to 13% candidates with a mean age of cancer emergence at 56 years. Ovarian carcinoma arises in an estimated 4 to 12% subjects with a mean age of tumor detection at 42.5 years wherein approximately 30% instances are discerned below <40 years [2,3].

Histological Elucidation

Individuals depicting a deleterious genomic mutation of lynch syndrome are accompanied with an enhanced emergence of malignancies with an elevated probability of colorectal carcinoma, endometrial carcinoma, gastric and ovarian carcinoma. Adenomas associated with lynch syndrome can rapidly metamorphose into carcinoma, in contrast to adenomas un-associated with the syndrome.

Characteristic tumor phenotypes are observed such as poorly differentiated, medullary-type carcinoma, mucinous adenocarcinoma, signet ring cells and a Crohn's like reaction accompanied with infiltrating lymphocytes (Fig. 1-10) [4].

Figure 1: Lynch syndrome demonstrates glandular epithelium with nuclear hyperplasia, hyperchromasia, nuclear overlapping, anisocytosis and mitotic.

Figure 2: Lynch syndrome demonstrating overlapping, hyperplastic and hyperchromatic nuclei admixed with tumour infiltrating lymphocytes.

Figure 3: Lynch syndrome depicting numerous dysplastic glands lined by atypical columnar epithelium with hyperchromatic nuclei and mitotic.

Figure 4: Lynch syndrome delineating proficient immune reactivity for cogent mismatch repair genes.

Figure 5: Lynch syndrome depicting proficient immune reactivity for comprehensive mismatch repair proteins.

Figure 6: Lynch syndrome demonstrating the concurrence of endometrial carcinoma with atypical endometrial glands lined by aberrant columnar epithelium.

Figure 7: Lynch syndrome enunciating specific, adenomatous precursor polyps.

Figure 8: Lynch syndrome exhibiting cogent, adenomatous precursor polyps.

Figure 9: Lynch syndrome exemplifying an immune reactivity for MSH6.

Figure 10: Lynch syndrome enunciating an immune reactivity for PMS2.

Differential Diagnosis

Lynch syndrome requires a segregation from Attenuated Familial Adenomatous Polyposis (AFAP), an autosomal dominant condition with a milder representation than Familial Adenomatous Polyposis (FAP), engendered by a genomic variant of Adenomatous Polyposis Coli (APC) gene. The disorder demonstrates a delayed onset and a diminished quantification of adenomatous polyps, in contrast to classic Familial Adenomatous Polyposis (FAP). Typically, polyps are quantifiable beneath <100. Additionally, gastric and duodenal polyps are cogitated although commonly discerned extra- colonic manifestations can be absent AFAP [3,4]. Lynch syndrome requires a demarcation from Turcot's syndrome, especially in individuals delineating a colorectal carcinoma or adenomas in addition to central nervous system tumors. Genomic variants of APC demonstrate numerous adenomatous polyps, in addition to enumerable polyps delineated with Turcot's syndrome and variant APC or a Turcot's syndrome due to variant Mismatch Repair (MMR) genes. Segregation from MUTYH associated polyposis is required. Bi-allelic variants of MUTYH gene are denominated in multiple adenomatous polyposis. Genomic variants of MUTYH are discerned within approximately 30% of subjects, depict around 15 polyps to 100 polyps, or a miniature percentage of classic instances of FAP devoid of specific, identifiable genomic variant of APC or in individuals with a cogent family history of colorectal carcinoma in the absence of multiple adenomatous polyps [2,4]. Differentiation from MSH3 related susceptibility to polyposis and colorectal carcinoma is necessitated. Bi-allelic germline MSH3 mutations are infrequently associated with early onset colorectal carcinomas and multiple adenomatous polyps. Separation from NTHL1 mutation susceptible polyposis and colorectal carcinomas is required. The condition is discerned in families with autosomal recessive conditions with inherited polyposis along with an enhanced possibility of colorectal carcinomas, which commonly emerges betwixt 40 years to 65 years.

Quantifiable polyps vary from one to exceeding >50 (Table 1) [2,4]. Demarcation of lynch syndrome is required from POLE mutation susceptible instances of colorectal carcinoma which demonstrate an enhanced possible occurrence. Quantifiable polyps can vary from a few to several lesions. Additional categories of carcinoma such as endometrial, ovarian, ureter, gastric and astrocytoma can be enunciated in association with POLE genetic mutation. Accompanying endometrial carcinomas are Microsatellite Instability-High (MSI-H) or Microsatellite Stable (MSS) [2,3]. POLD1 related emergence is an exceptional factor engendering hereditary colorectal carcinoma. Li-Fraumeni syndrome can incur colorectal and additional gastrointestinal cancers, a component originating due to variants of TP53 gene. Hereditary diffuse gastric cancer as an autosomal dominant condition is engendered by genomic variants of CDH1 and typically enunciates adenocarcinomas [3,4]. Hereditary breast and ovarian cancer syndrome contingent to BRCA1/BRCA2 genetic mutation is an autosomal dominant condition.

Aforementioned disorders mandate a segregation from lynch syndrome. Several autosomal dominant disorders are associated with enhanced possible occurrence of hamartomatous polyps and colorectal carcinoma, which can be discerned with cogent extra-colonic manifestations accompanied by hamartomatous polyps, instead of adenomatous polyps. Conditions such as juvenile polyposis syndrome demonstrating SMADA4 and BMPR1A genetic mutations, Peutz-Jeghers syndrome delineating STK11 genetic mutation and PTEN hamartomatous syndrome as designated with Cowden syndrome and Bannayan- Riley- Ruvalcaba syndrome depicting PTEN genomic variations require a demarcation from lynch syndrome [2,4].

Gene	Proportion of Lynch Syndrome	Genetic sequence analysis	Gene targeted deletion/ duplication analysis
MLH1	50%	90-95%	5-10%
MSH2	40%	<80%	>20%
MSH6	7-10%	>95%	<5%
PMS2	<5%	40-50%	40-50%
EPCAM	1-3%	Unsatisfactory	100%
Unknown		NA	

Table 1: Molecular genetic testing of lynch syndrome.

Surveillance Protocols

Recommended surveillance for reducing possible emergence of carcinomas within carriers of lynch syndrome with genetic mutations of MLH1, MSH2, MSH6, PMS2, and EPCAM variants are ≈Colonoscopy commencing at 20 years to 25 years, repeated annually or every 2 years to 5 years, preceding the initial discernment of colorectal carcinoma, particularly in instances detected prior to 25 years. Colectomy is recommended in subjects delineating a colon cancer or an advanced stage of colonic adenoma which is surgically unamenable to resection. With advancements in surgical manoeuvres, a segmental or extended segmental colectomy can be adopted in managing definitive colorectal adenocarcinoma and/or adenomatous polyps, contingent to individual preferences. Postoperatively, follow up of cogent colonic surveillance with endoscopic examination of the lower gastrointestinal tract is required annually or once in two years in instances where surveillance measures are inadequate [5]. ≈Evaluation of uterine endometrium and ovaries can be approached with a pelvic examination, transvaginal ultrasound, endometrial aspiration and/ or a serum assay of CA-125 in individual instances. However, the efficacy of aforesaid regimen remains undetermined. Abnormal uterine or vaginal haemorrhage necessitates immediate evaluation. Total hysterectomy with salpingo-oophorectomy is recommended in candidates with a complete family [5]. ≈Evaluation of extra-

colonic carcinomas demonstrating mutations of MLH1, MSH2, EPCAM chromosomes and contingent genetic carriers necessitate assessment. Probable emergence of adjunctive lynch syndrome related malignancies is minimal within MSH6 and PMS2 genetic carriers. On account of limited data, National Comprehensive Cancer Network (NCCN) recommendations for the management for MSH6 and PMS2 related carcinomas is limited. Upper gastrointestinal endoscopy with esophagogastroduodenoscopy and an extended duodenoscopy can be adopted every three to five years commencing at 30 years to 35 years in a select category of individuals or family members of Asian descent. Investigation and treatment of concomitant infection with *Helicobacter pylori* is mandated [5,6]. ~Routine analysis of a urine specimen is commenced at 30 years to 35 years on an annual basis. Optimal age for commencement of screening of urinary tract carcinomas is as yet uncertain although aforesaid malignancies are infrequent prior to 30 years. ~Additional surveillance for central nervous system or brain tumors and pancreatic malignancies accompanied by an annual physical and neurological evaluation is advantageous, commencing at 25 years to 30 years. Despite enhanced proportion of pancreatic cancer, efficacious screening strategies and treatment guidelines are lacking [5,6]. ~Enhanced possibility of occurrence of carcinoma breast in individuals with lynch syndrome is undetermined, therefore screening for carcinoma breast is contingent to cogent personal and family history [6].

Investigative Assay

Screening procedures with subsequent evaluation of germline mutations can be satisfactorily adopted to categorize a lynch syndrome. Subjects demonstrating possible emergence of lynch syndrome can be discerned with pertinent personal or family history of malignant emergence and appropriate concordance with clinical, screening criterion such as the Amsterdam II criterion and Revised Bethesda guidelines. Colorectal carcinomas demonstrating a microsatellite instability within tumor tissue samples can exemplify lynch syndrome, if associated with a concomitant germline mutation within a mismatch repair gene. Currently applicable screening guidelines for ascertainment of lynch syndrome are contingent to National Comprehensive Cancer Network (NCCN) which recommends an immune histochemical staining of the mismatch repair proteins cogitated within colorectal carcinoma, especially in subjects beneath <70 years, subjects with colorectal carcinoma exceeding 70 years and fulfilling Bethesda criterion and individuals demonstrating endometrial carcinoma below <50 years. Common methodologies adopted for screening of lynch syndrome are immune histochemical staining and /or assessment of microsatellite instability. Concordance betwixt the dual sensitive and specific modes of evaluation is significant and accompanied by a false negative rate of around 5 to 10% [6,7]. Immune histochemical evaluation is performed upon a tumor tissue sample in order to discern protein exemplification, usually encoded by mismatch repair genes. Immune reactivity for the entire panel of mismatch repair proteins is indicative

of absence of a mismatch repair genetic mutation. Normal outcomes are referred to as “mismatch repair proficient”. Immune non reactivity for a singular mismatch repair protein is referred to as “mismatch repair deficient” and germline genetic evaluation is required in such instances [7]. Immune histochemical reactions singularly determining mismatch repair protein MLH1 or in conjunction with PMS2, are aberrant in colorectal carcinoma and mandate a successive evaluation of BRAF V600E genomic mutation or hypo-methylation of MLH1 promoter, enunciated within the blood or normal tissue. Aforesaid immune reactivity is suggestive of a sporadic colorectal cancer, instead of a lynch syndrome. Immune non reactivity for aforesaid genomic panel requires assessment of germline mutation for lynch syndrome [7]. Micro-Satellite Instability (MSI) is a screening modality adopted for assessing lynch syndrome and characteristically demonstrates variations in length of repetitive DNA sequences, fragments denominated as “microsatellites” within the human genome which emerge on account of decimation of mismatch repair activity. Identification of techniques for assaying microsatellite instability incorporates the utilization of nucleotide biomarkers. Tumors depicting a certain proportion of atypical microsatellite repeat markers are contemplated to be Microsatellite Instability-High (MSI-H) whereas mismatch repair proficient tumors are generally equivalent to Microsatellite Instability-Low (MSI-L) [7]. Majority of cancers associated with lynch syndrome are Microsatellite Instability-High (MSI-H). Although aforesaid mutational pattern can be observed with sporadic colorectal carcinomas, germline chromosomal evaluation is recommended in Microsatellite Instability-High (MSI-H) carcinomas. Amidst the sporadic colorectal carcinomas, an estimated 10 to 15% neoplasms exhibit a deficiency of minimally a singular mismatch repair protein and/or occur as microsatellite stability-high tumors, generally on account of abnormal methylation of MLH1 gene promoter region and may not configure as a component of lynch syndrome. Therefore, evaluation of microsatellite instability and /or singular immune histochemical assay may be inadequate to discern lynch syndrome and mandates a successive germline mutational analysis [7,8]. Germline mutation evaluation is accomplished by DNA sequencing and enlarged analysis of genetic rearrangement. Genetic assessment requires a preceding genetic counselling on account of complexities within selection of test subjects. Individuals with aberrant immune-histochemical reactions and/or atypical microsatellite instability evaluation wherein germline investigations are devoid of a mutation can arise due to a duplicate somatic mismatch repair genetic mutations within the tumor DNA or can appear due to undetected lynch syndrome [7,8]. Criterion for clinical evaluation are contingent to personal and family history. Assessment for lynch syndrome is commenced with a pertinent family history of carcinomas, comprised of maternal and paternal relatives and minimally three generations of first, second and third degree relatives. A comprehensive list of emergent malignancies is required along with initial age of diagnosis [7,8]. Genetic evaluation pertaining to lynch syndrome is recommended in individuals with cogent Amsterdam II criterion, revised Bethesda guidelines, endometrial cancer discerned beneath 50 years and lynch syndrome diagnosed within the family [7,8]. Genetic investigation is contemplated in subjects with a minimal 5% possibility of lynch

syndrome upon employment of specific predictions models such as MMRpro, PREMM or MMRpredict. Amsterdam II criterion are comprised of relatives with a lynch syndrome related carcinoma such as colorectal, endometrial, small intestinal, ureter and renal pelvis exceeding three, with a singular relative being a first to fulfil the following criterion ≈Successive generations implicated exceeding two ≈A singular subject as a first degree relative of accompanying two individuals. ≈Relatives discerned with lynch syndrome beneath <50 years exceeding one ≈An absence of evidence of familial adenomatous polyposis. Revised Bethesda Guidelines are constituted of ≈Colorectal carcinoma detected in subjects beneath <50 years. ≈Occurrence of synchronous or metachronous, colorectal or adjunctive lynch syndrome related malignancies, irrespective of age. ≈Colorectal carcinoma demonstrating histological features indicative of microsatellite instability-high carcinomas such as the appearance of tumor infiltrating lymphocytes, Crohn's like lymphocytic reaction, mucinous or signet ring differentiation or a distinctive medullary growth pattern [7,8]. ≈Colorectal carcinoma discerned in a subject with a singular or additional first degree relative demonstrating a lynch syndrome related carcinoma, with minimally a singular carcinoma detected preceding <50 years. ≈Colorectal carcinoma detected in individuals with two or more first or second degree relatives delineating lynch syndrome related malignancies, irrespective of age of emergence. Lynch syndrome related carcinomas are comprised of colorectal, endometrial, gastric, ovarian, pancreatic, ureter, renal pelvis, biliary tract, small intestinal and brain cancer as designated with glioblastoma, simulated in Turcot's syndrome, in addition to sebaceous gland adenomas and keratoacanthoma, simulated in Muir-Torre syndrome [7]. Applicability of Amsterdam criterion and Bethesda guidelines to identify subjects with lynch syndrome discern malignancies in an estimated 50% whereas around 50% of subjects fulfilling diagnostic criterion are devoid of lynch syndrome. Individuals identified by tumor evaluation with immune histochemical techniques and/or microsatellite instability assessment or fulfilling evaluation criterion are recommended to adopt specific genetic assay or multi gene analysis of implicated family members. However, in the absence of implicated family members, investigation of unaffected individuals can be contemplated [7,8].

Therapeutic Options

Optimal therapy of lynch syndrome is contingent to ascertainment of cogent personal and family history. Guidelines of potential risk for emergence of lynch syndrome within carriers are associated with declining cancer mortality [7,8]. Efficacy of administering Non-Steroidal Anti Inflammatory Drugs (NSAIDs) in candidates of lynch syndrome requires assessment. Administration of aspirin can decimate possible occurrence of colon cancer in lynch syndrome, although the optimal dose and duration is unspecified. Discernment of lynch syndrome is significant for assessing a possible occurrence of concurrent malignancies in family members. Thus, opportunities for appropriate evaluation, screening and surveillance with adequate genetic counselling require exploration and adoption [7,8].

Conclusion

Lynch syndrome is a frequently discerned hereditary cancer syndrome demonstrating the occurrence of colorectal carcinomas in around 80% subjects and endometrial cancers in nearly 60% individuals. Lynch syndrome is accompanied by germ line chromosomal mutation of one of the four Mismatch Repair (MMR) genes, enunciated as MLH1, MSH2, MSH6 or PMS2, which can be discerned with cogent immune histochemical reactions or evaluation of Microsatellite Instability (MSI).

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