Extracolonic Manifestations of Lynch Syndrome

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Abstract

Keywords

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- mismatch repair genes
- atypical phenotype

Lynch syndrome has classically been defined by several predominant malignancies. Initial clinical criteria for diagnosis of Lynch syndrome would miss 40% of affected individuals. As time has passed, our understanding of Lynch syndrome has evolved and will continue to do so. The number of cancer types that are included in the Lynch phenotype is growing. This has allowed clinicians to redefine Lynch syndrome, at risk populations, screening needs, and diagnostic criteria. Inclusion of extracolonic malignancies and alternative genetic pathways gives new insight into the true prevalence and penetrance of Lynch syndrome.

Objectives: Upon completion of this article, the reader should be able to summarize well-documented characteristics of Lynch syndrome, as well as recent data serving to redefine the role of extracolonic malignancies.

History

Lynch syndrome has been a source of variability regarding its component malignancies and phenotypical presentation since its original description by Aldred Warthin in 1913.¹ Interestingly, the described kindreds were afflicted by predominantly gastric and endometrial cancers. Only two patients were diagnosed with colorectal cancer (CRC). Fifty-years later, due to the work and dedication of Henry Lynch and his coworkers, a more recognizable clinical entity emerged, and it continues to evolve to this day. In addition, countless other authors have since contributed to defining the genetic and molecular building blocks that have led to our current understanding and available testing techniques.

The natural history and evolution of Lynch syndrome has led to a “traditional” understanding of what one would expect to see regarding its definition and clinical characteristics. As such we would expect the predominant cancers to be colon cancer, endometrial cancer, and ovarian cancer, with multiple less “common” malignancies seen intermittently. In addition, the initial incidence of Lynch syndrome was thought to be relatively rare, a belief that is unfortunately still common today.

Widespread recognition of the “traditional” Lynch syndrome, has allowed significant advances in our understand-

ing of its incidence, identification, treatment, and clinical impact. Current studies conservatively suggest that Lynch syndrome may account for 2 to 10% of all colorectal cancers.² These estimates will likely change as more data becomes available in relation to the true nature of familial or hereditary colon cancers. These percentages should not be confused with the true prevalence of Lynch syndrome, which is defined not only by the incidence of colon cancers, but also by the presence of an evolving group of extracolonic malignancies. An alternative picture has emerged, that would appear to be much different than the initial description more than 40 years ago. With this evolution comes a need to update our ability to identify both at risk individuals, and those definitively affected by Lynch syndrome. Part of this process is redefining the role, incidence, and distribution of extracolonic malignancies, which appears to be different than what we once thought.

Extracolonic Malignancies

The traditional understanding of Lynch syndrome identified colon and rectal cancer, endometrial cancer, and ovarian cancer as part of the Lynch spectrum of malignancy. The remaining malignancies, gastric, urothelial/renal, brain, biliary, pancreatic, skin, and small bowel are known to occur with greater frequency within Lynch syndrome as compared with the general population, but have not been part of the traditional selection of Lynch cohorts. The specifics of colorectal and endometrial/ovarian malignancies as they relate to Lynch syndrome have been addressed in earlier articles in this

journal. The remaining Lynch associated malignancies have less data, but recent advances in our definition of Lynch patients and the underlying genetic mechanisms for this syndrome have improved our understanding of the Lynch phenotype.

Gastric Cancer

Initial investigations reported gastric cancer (GC) as the third most common Lynch syndrome-associated malignancy; in fact, it was the most common tumor Aldred Warthin described in 1913.^{1,3} In recent years, there has been periodic debate with regard to the role of GC in Lynch syndrome, with some consideration of eliminating surveillance/screening maneuvers. A likely reason for this is that GC is less frequently reported in studies; therefore, other cancers seem more prevalent. In fact, Amsterdam Criteria do not include GC; Lynch syndrome population studies have been based primarily on colon or endometrial cancers. As such, both of these cancers proved to be the prime determinants for selection of study populations.⁴

The specific MMR gene, geographic location, and ethnicity have proven to be far more important in defining the Lynch phenotype than once thought. When looking at Western compared with Eastern populations, distinct differences have been noted that must be kept in mind. Da Silva et al, upon assessing Brazilian populations, found that GC is in fact the second most common extracolonic malignancy. This is further supported by numerous Chinese studies showing it to be the most common extracolonic Lynch syndrome malignancy.⁴ In Western literature, the prevalence of GC within Lynch syndrome cohorts is substantial but it presents as third or fourth most common malignancy depending on the study population.⁵

There are also differences when looking at the mean ages of gastric cancer diagnosis. The Brazilian mean age at diagnosis was 53, the Japanese was 60, North American was 60, and the outlier was Korea at 46 years of age.⁴⁻⁷ The Korean population also revealed different patterns than previously seen. When corrected for the higher endemic risk of GC, Korean data pointed to a 11.5-fold and 5.5-fold increased risk at ages 30 and 40, respectively, for patients in families meeting Amsterdam Criteria.⁷ When taken as a whole, the relative risk for mutation carriers was found to be 3.2 times the general population. Similarly, the lifetime risks, when corrected for endemic population risk, were 14% for North American studies, 19% for Finnish studies, 30% for the Korean studies, and the Brazilian literature indicated a near 100-fold increased risk of GC in association with Lynch syndrome.^{4,5,7}

The involved genes also differ depending on the study population and geographic circumstance. Many studies, Western included, indicate MSH2 as most commonly associated with GC and extracolonic malignancies. However, almost all GC studied by Park et al reveal MSH1 mutations as the source, which is unique to the Korean population.⁷ In a similar light, Akiyama et al found atypical Lynch phenotypes that ultimately did not meet Amsterdam Criteria, but revealed MSH6 mutations as causative for gastric and rectal cancers.⁶

Consideration should also be given for the possible role of CHEK2 in GC and Lynch-like phenotypes as seen in the Polish and Eastern European populations, but more data are needed.⁸

There should be no mistake regarding the role of GC in Lynch syndrome. The only question that remains is how to effectively define and survey the at risk populations. The current data would suggest variable MMR mutational expression, alternate genetic pathways, "modifier" genes, and variability based upon geography and ethnicity. These findings serve to make that goal difficult. At the same time, we should not attribute Lynch-associated GC to underlying endemic risks of a general population. In as much as CRC is much more common in the United States, Lynch syndrome contributes substantial additive risk for CRC and should not be seen as similar to the general population risk.

Breast Cancer

Inherited susceptibility to breast cancer (BrC) has been well documented; with BRCA I and BRCA II representing what would seem to be the prototype. Even so, in so much as BRCA represents a completely separate entity, it shares some phenotypical overlap with Lynch syndrome that may prompt assessment for both processes. Though BRCA represents the most studied and understood mechanism, recent findings have introduced other genetic influences that have changed our understanding of BrC causation, the scope of those affected, and other possible mutational mechanisms.

There has been considerable debate as to the role of BrC in Lynch syndrome, as well as its role in possible Lynch-like processes. Original descriptions of Lynch syndrome did note BrC sporadically, but it was not felt to be enough to warrant inclusion in the extracolonic manifestations. There have also been several studies in the early 1990s documenting MSI in breast tumors. One such study indicated 39% of lobular carcinoma and 13% of ductal carcinoma exhibited MSI. However, at that time, no data looked at the association of MSI and MMR mutations in the context of Lynch syndrome.⁹

Since that time, as our understanding has improved, the role of BrC has changed and strong consideration should be given to it as part of Lynch syndrome's spectrum of cancers. There are several studies that do provide data finding BrC in conjunction with both MMR mutations and other alternate mutations that might indicate direct and indirect links to Lynch syndrome.

Jensen et al examined Danish populations, retrospectively, with known MMR mutations and refined their search to include BrC. They identified 164 families with disease predisposing MMR mutations. Ninety-seven fulfilled Amsterdam Criteria. Forty-seven patients were found to have BrC; however, due to uncertain carrier status of first-degree relatives and apparent inability to confirm such, 27 were not further investigated. The remaining confirmed MMR mutation carriers were analyzed, revealing that 44% of the tumors exhibited loss of MMR protein expression with a mean age at diagnosis of 51. The causal MMR mutations were MSH6 (57%) and MSH2 (43%).¹⁰ In addition, further histological

assessment revealed 50% of the tumors showed tumor infiltration of lymphocytes, similar to the characteristic features seen in CRC.

In further support of this promising data, Risinger et al was also able to define BrC in definitive MLH1 mutation carriers. This too revealed confirmatory MSI within the tumors, though the study was very limited.⁹ There have also been at least two reported cases of males with BrC, both exhibiting loss of MLH1 expression and subsequent MSI.¹¹

In 2001, Scott et al found BrC to be prominent within the Lynch syndrome patients studied, representing the second most common extracolonic malignancy. This study revealed the majority to be associated with the MLH1 mutation.¹² Subsequent to that study, somewhat conflicting data was reported by Vasen et al. They retrospectively reviewed their registry of 200 families, and found the relative risk of BrC was not supported among their MMR mutation carriers. However, for those affected by BrC, the mean age of diagnosis was 46 years of age and they too noted widespread MSI (four MLH1 and three MSH2 mutations) within the breast tumors that were seen. They hypothesized that perhaps the MMR mutations served as an accelerant to the accumulation of mutations in different tissues. This may not necessarily lead to certain distinct tumors occurring, but rather rapid/early development of many tumor types, of which BrC would be included.¹³

The aforementioned studies all looked at known MMR pathways to explain a possible association between Lynch syndrome and BrC. There is data involving CHEK2 variants that suggests possible alternate pathways to BrC development in a Lynch-like process. Two variants (1100delC and I157T) have been found to be potential candidates for not only BrC, but also Lynch-associated malignancies.¹⁴ Meijers-Heijboer et al found 2.6% of CHEK2 mutation carriers' also harbored definitive MMR mutations. Additionally, of those patients found to have both CRC and BrC, 19% fulfilled AC I in the face of numerous other cancers that would be traditionally Lynch related.¹⁵ Not all family members with these cancers harbored a mutation while others did, prompting the question for the possible role of CHEK2 as a comodifier with another unknown gene(s). Though not the primary endpoint, another consideration is a Lynch-like process with higher incidences of BrC.

The overlap of CHEK2 and MMR mutations is a strong indicator of some relationship, and that is further supported in other studies. Waseilewskil et al found a 4.2% overlap, and noted 64% of the CHEK2 cohort fulfilled Amsterdam Criteria. Of those definitive Lynch patients, 7% harbored BrC.¹⁶ Similarly, Suchy et al found 8.8% of the CHEK2 cohort harbored MMR mutations.⁸ The notable weaknesses of these findings are the small populations studied; the criteria used to identify Lynch syndrome do not specifically include BrC; and the unclear role of CHEK2 as a modifier, accessory susceptibility gene, or completely separate hereditary syndrome. The cumulative data does point to some type of relationship between BrC and Lynch syndrome. This role will likely be better defined in time and should not be relegated to chance.

Urothelial and Other Urological Cancers

Urothelial cancer (UC) of the upper urinary tract is a well-described extracolonic malignancy of Lynch syndrome. These normally represent 5% of the upper UC within the general population. The presence of Lynch syndrome predisposes the affected patients to a 20-fold increase in these cancers. More specifically, prior studies have suggested this risk to be 17 times the incidence for renal pelvis/calycal cancer and 22 times the incidence for ureteral cancers.¹⁷ This would correspond to a cumulative lifetime risk of 2.6 to 4.0%, with a mean age at diagnosis of 55 years in Lynch syndrome patients.¹⁸

When looking at what is known, there are several studies that would indicate MSH2 mutations account for a majority of UC, with diagnoses rarely before age 40.^{19–21} Watson et al not only suggest a sevenfold higher risk for MSH2 mutations, but also cite gender as a modifier of UC prevalence. Their study indicated a 1.6-fold increased risk in males compared with females. When viewed together, this corresponded to a lifetime risk of 28% for male/MSH2 carriers, which is highest between the ages of 50 to 70.²⁰

There are, however, conflicting reports showing MLH1 and MSH6 mutations as responsible entities. In keeping with the so-called MSH6 mutation carrier's "atypical" phenotype, the literature also contains reports where MSH6 mutations accounted for 10% of UC, with male risk equal to female risk, and later onset at 70 years of age.²¹ Rather than clearly defining a source mutation as the key causative factor, the literature points to variable presentations for different MMR mutations. This underscores the need to continue defining at risk populations.

A potential diagnostic tool is tumor immunohistochemical staining, which has been shown to be effective in detecting MMR mutations in 78 to 87% of upper UC that are known to have microsatellite instability.¹⁸ If IHC were applied more globally, it may not only help identify at risk/affected populations, but also better define responsible mutations.

What this data does not address is the potential involvement of the bladder or prostate gland. Until relatively recently, no obvious association was described for bladder cancer (BC) or prostate cancer (PrC) within the spectrum of Lynch-related malignancies. There are several reasons for this. First, neither cancer type is included in Amsterdam Criteria, which are highly specific, are now known to potentially miss 30 to 40% of affected carriers, and have been used as selection criteria for studies that look at the incidence of BC and PrC in Lynch syndrome. Secondly, use of more common cancers (CRC or endometrial cancers) to identify potential Lynch syndrome patients results in potential ascertainment bias based upon the relative rarity of BC or PrC in comparison. Finally, the prevalent nature of those tumors in the general population, coupled with clinicians lack of awareness of "less common" Lynch-related malignancies, would predispose to limited identification of hereditary influences, without a very high index of suspicion.

Kastrinos et al studied 1914 unrelated cancer patients who were undergoing genetic testing. Ultimately, 285 (15%) were found to have identifiable MMR mutations (MLH1 and

MSH2). Interestingly, of those mutation carriers, only 63% fulfilled revised Amsterdam Criteria. Their data revealed BC to account for 33% of all UCs and MSH2 accounted for 73% of the mutations found.²² Similarly, Gylling et al investigated 150 tumors from MMR mutation carriers from their nationwide Finnish Registry. They found that BC represented 36% of the UCs identified, with a mean age at diagnosis of 55. Notably, their data indicated that MLH1 accounted for 79% of the mutations.²³ Overall, BC's inclusion in Lynch syndrome (or potential Lynch-like processes) warrants consideration, though further studies are needed.

PrC represents an ambiguous entity due to its prevalent nature and established familial associations (15 to 20% of all PrC) within the general population. There is also little question as to the role of genetic factors, already implicated in 40% of prostate cancers diagnosed at or below 50 years of age.²⁴

Hereditary influences, specifically the role of MMR mutations, and association with Lynch syndrome is something that was once dismissed. Recently, however, that consideration has garnered support, with some authors advocating its inclusion in the syndrome. This is based upon our improved understanding/testing of MMR genes and of other possible mutational events.

The past 10 years has spurred reports and data, albeit somewhat limited, that provides some proof that MMR mutational pathways do exist and PrC has some role in Lynch syndrome. Grindedal et al studied 106 men with definitive MMR mutations and PrC represented 9% of the cancer types (mean age of diagnosis was 60). Furthermore, it was noted that MSH6 and PMS2 deficiencies were more frequently responsible, with MSH2 making up the remainder. Kaplan-Meier analysis of the Norwegian population indicated that the cumulative risk of PrC was 30% by age 70 for mutation carriers as compared with 8% in the general population.²⁵ Goecke et al studied MMR mutation carriers and their relatives with a cancer diagnosis. In this cohort, MSH2-deficient PrC was found to be the most common cancer not previously associated with Lynch syndrome.¹⁹ In 2010, a Brazilian study evaluated extracolonic malignancies of Lynch syndrome. Their results revealed PrC to be the most common (21%) extracolonic tumor within the Lynch syndrome cohort. They did not assess those tumors for MMR deficiencies for unknown reasons, and made assumptions based upon ages of diagnosis, which has been proven to be a poor indicator of Lynch syndrome.⁴ Scott et al may have provided indirect support of a MMR pathway in their assessment of 95 families with HNPCC. PrC was similar in incidence to other known Lynch-related malignancies, but was highly represented within the mutation-negative group studied.¹² The higher incidence of PrC in MMR-deficient patients in varied populations suggests an association between PrC and Lynch syndrome, which deserves further study.

PrC may also develop through non-MMR mutation pathways. PrC risks have been found to be significantly elevated and firmly associated with the two variant mutations of CHEK2.^{14,26} This may represent some type of direct association with Lynch syndrome, an accessory pathway, or an altogether alternate hereditary entity.

Pancreaticobiliary Cancer

Pancreaticobiliary cancers (PbCs) include cancers of the pancreas, bile duct, ampulla of Vater, and gallbladder. Biliary cancers are relatively rare malignancies accounting for only 1 to 2% of all cancers in the United States, whose mean age at diagnosis is 65, with a higher incidence in females.²⁷ Notable exceptions include Native American Indians and Hispanic populations who have a fourfold increased risk. In contrast, the worldwide incidence of PbC is higher and based on geographic differences. PbC is much more common in the general populations of India, Korea, Japan, Czech Republic, Slovakia, Spain, Columbia, Chile, Peru, Bolivia, and Ecuador. On the other hand, pancreatic cancer is more common in the United States and is the fourth most common cause of cancer-related death. The mean age of diagnosis is noted to be 67 years of age. Most cases are sporadic, but it is estimated that up to 10% are related to hereditary factors.²⁸ For purposes of discussion, the cancers will henceforth be referred to as PbC as many studies did not differentiate the exact sites or cell type.

The endemic prevalence of the cancers do not negate the risks of PbC in association with Lynch syndrome, but rather they are additive. As such, it is estimated that Lynch syndrome potentiates the risk of PbC by 4 to 6 times.²⁹ Once again, those estimates have historically been based upon data derived from the selection of families with primarily CRC rather than PbC.

Kastrinos et al evaluated the incidence of PbC among families with germ-line MMR mutations. In this cohort, 21% of the MMR mutational carriers developed PbC (66% MSH2, 28% MLH1, and 7% MSH6), which approximates a ninefold increased risk of PbC as compared with the general population. There was no gender predilection and the mean age at diagnosis was 51. They did note a trend of increasing risk with age between the ages of 20 to 70 years. The highest relative risk occurred between the ages of 20 to 50.²⁸ In another study, Song et al found PbC was the third most common malignancy in HNPCC patients who met clinical diagnostic criteria. These patients had a fourfold increased cumulative risk compared with the general population and a mean age of 39 at diagnosis.³⁰ This is similar to Aarnio et al who found 4% of extracolonic cancers (their fifth most common tumor type) were PbC in HNPCC patients, constituting a lifetime risk of 18%.³¹ Barrow et al, while noting 4% of the extracolonic tumors were PbC (mean age 49 years), found MLH1 mutations conferred a 13.5 times higher risk. Conversely, numerous other reports suggest MSH2 as responsible for the majority of PbC, further underscoring the potential variable phenotypes for individual germ-line MMR mutations.³²

Documentation of the exact locations of the malignancies is a potential shortfall of many of the literature reports. Some cite the biliary ducts and ampulla as the most common sites, while others simply refer to the biliary tract. Though not directly related, this issue also underscores the difficulty of localization, diagnosis, and screening options for those deemed at risk. Noninvasive means such as ultrasound are less likely to identify early pathology, and invasive means

come with potential risks. In this regard, Roa et al provided additional data supporting use of IHC to accurately determine PbC MSI, with all MSI-high tumors showing altered staining patterns.³³ IHC may represent a potential tool, much like it is used on colon neoplasms, to aid in identification, screening, or surveying individuals at risk for Lynch syndrome.

Since Dr. Lynch's reports on PbC those many years ago, there have been conflicting reports regarding its prevalence and risks. Advances in our understanding and improved awareness have led to numerous current studies that firmly entrench the entire spectrum of PbC within the Lynch syndrome phenotype. More studies that identify the most likely locations of Lynch associated PbC and the usefulness of screening at risk patients are needed.

Small Bowel Cancer

Small bowel cancers (SBCs) account for 1 to 2% of all gastrointestinal (GI) cancers, with a lifetime risk estimated to be 0.01% within the general population.³¹ SBC in association with Lynch syndrome varies in reported incidence, but numerous studies indicate a lifetime risk of 1 to 4%.³⁴ In the past, the primary difficulty in determining its prevalence has been poor screening modalities, the limited capture of Amsterdam Criteria, and selection of cohorts based upon CRC or endometrial cancers. Since then, our diagnostic tools/techniques and knowledge base have improved, hopefully giving a clearer picture of what this extracolonic malignancy poses as a risk.

Multiple studies have examined characteristics of Lynch associated SBC. Kate et al found SBC represented 2% of the extracolonic cancers with a median age of 52 years, and determined that 1 in 25 germ-line MMR mutation carriers will develop SBC. Their data did not show a predilection for MSH1 or MSH2. The anatomical distribution (43% duodenum, 33% jejunum, 7% ileum) was consistent with other reports. In addition, in 54% of the patients, SBC represented the index cancer for Lynch syndrome.³⁴ Schulmann et al reported on 32 Lynch syndrome-associated SBCs. They found the mean age at diagnosis to be 39 (20 years earlier than the general population), and the distribution was proximal (47% duodenal, 29% jejunum, 12% ileal). In this cohort as well, SBC represented the index Lynch cancer in 50%. In addition to the commonly seen adenocarcinoma, small bowel carcinoid and stromal tumors were also found to be MMR deficient. The germ-line mutations favored MLH1 (59% MLH1, 37% MSH2, and 4% MSH6), which is similar to other reports.³⁵ Interestingly, only 50% of the SBCs met Amsterdam Criteria, and no EpCAM (epithelial cell adhesion molecule) analysis was performed.

With advances in our diagnostic capabilities, assessment or surveillance of the small bowel is safer and more efficient. SBC as a Lynch malignancy is not in question, but its overall prevalence has been widely reported. Despite the markedly elevated relative risk associated with Lynch, many look at the estimated lifetime risk (1–4%), which may seem relatively low. This can give a false sense of security, particularly in light of small studies and limited data. When looking at recent literature, the mean age of diagnosis is at least 20 years earlier than the general population. Age-specific analyses have not

been done, and these may be a better estimate of risk. This is especially true as the aforementioned studies also found 48 to 50% of the SBCs represented the index cancer rather than CRC. In addition, with the proximal nature, endoscopy is a reasonable tool for screening. Biopsy and ultrasound, if coupled with capsule endoscopy, pose safe, reasonable, and accurate alternatives of assessment.

Brain Cancers

According to SEER (National Cancer Institute) 2004–2008 data, primary brain cancers (BCc) confer a lifetime risk of 0.3–.6% for the general population with the median age at diagnosis being 64. Glioblastoma multiforme (GBM) and astrocytoma represent 85% of these tumor types. Though still relatively rare, Lynch syndrome confers a marked fourfold increased lifetime risk for BCs, with average age at diagnosis ranging from 25 to 38.^{5,20,23} Gliomas have been the most widely reported Lynch associated brain tumors, but one longstanding limitation has been sparse reporting of the exact cell types and the overall relative rarity of these tumors. A Turcot syndrome variant represents a specific entity associated with MMR mutations and thus Lynch syndrome. It is characterized by adenomatous colon polyps, CRC, and elevated risk of glioblastoma.

Recent literature identifies multiple cell types to be associated with Lynch syndrome MMR mutational carriers. The spectrum includes GBM, astrocytoma, meningioma, acoustic neuroma, and neuroblastoma.^{5,36} There have also been somewhat conflicting reports regarding the gene-specific risks. Early studies indicated MLH1 mutation carriers had higher cumulative risks of BC, but that has been contradicted in several current reports suggesting MSH2 mutational carriers confer much higher risks.^{23,32,37}

There are isolated reports that indicate another potential accessory Lynch pathway or modifier through CHEK2. The limited information thus far describes MMR mutational carriers (Lynch phenotypes) with an additional germ-line CHEK2 mutation in the presence of BC (meningioma and GBM).^{14,34}

The mixed information regarding MMR mutational specificity, coupled with small numbers studied and other germ-line events, undoubtedly add to the difficulty of detection. Watson et al, among other authors, hypothesize the true prevalence and characteristics related to Lynch syndrome may be masked or only partially realized. This is due to rarity, the young age of onset (Watson et al report 26% being diagnosed < 25 years old), as well as the high mortality (90% mortality with 23% dead before age 25). Therefore, a Lynch syndrome patient who develops BC has a dramatically reduced chance of undergoing genetic assessment, developing CRC and other cancers, or having children.²⁰ This would clearly limit our ability to identify and study those specific populations with BC as the primary selection criteria.

Skin Cancer

There has been numerous skin cancers described in Lynch syndrome cohorts. The most notable is that of the Muir-Torre

variant. It was first described in the 1960s and associated with the Lynch phenotype.³⁸ The characteristic Lynch variant findings include at least one sebaceous neoplasm (sebaceous adenoma, sebaceous epithelioma, sebaceous adenocarcinoma, keratoacanthoma, and squamous cell carcinoma) and at least one visceral malignancy (typically gastrointestinal and urological). The median age of skin cancer diagnosis has been reported to be 53, and was thought to represent 2% of extracolonic presentations. Older studies indicated it to be associated solely with MSH2 mutational carriers.^{19,38,39}

As alluded to earlier, the spectrum and variability of Lynch syndrome has evolved over time. Since the identification of MSH6 mutation as a pathway for Lynch syndrome, it has often been associated with an attenuated phenotype. It should also be noted that our understanding of that scope is still in its infancy. With that in mind, Muir-Torre has now been linked to germ-line MSH6 mutations.³⁸ This finding lends itself to the possibility that prior to this, other similar cases were undiagnosed, missed by traditional testing methods, and most certainly missed when assessing cohorts based upon Amsterdam Criteria.

Other skin-related malignancies have also been found within Lynch syndrome families. Recent literature has documented basal cell carcinoma, epidermoid carcinomas, and cutaneous sarcoma in Lynch syndrome families.⁴⁰ This does need to be viewed with caution, due to small study designs and possible ascertainment bias. Those authors found skin cancers represented 3 to 5% of the extracolonic cancers.^{4,32,41} More studies are required to determine whether Lynch syndrome confers increased risk of skin cancer outside the Muir-Torre variant.

Hematopoietic Malignancies

Hematologic malignancies have not traditionally been associated with Lynch syndrome, nor considered within the diagnostic criteria. Over the last few decades there have been increasing reports of blood-borne malignancies within Lynch syndrome families scattered throughout the literature.

Some of the more commonly reported hematopoietic malignancies, in conjunction with Lynch syndrome patients, have included leukemia (acute and chronic lymphocytic leukemia), myeloma, and non-Hodgkin's lymphoma. The relative incidence among extracolonic Lynch malignancies ranges between 3 to 7%, with MSH2 more frequently identified as the source mutation.^{4,12,30,42–44} More in-depth data or specifics regarding the spectrum of malignancies is lacking.

Until recently, the relative rarity of these cancers within studied cohorts was likely due to several factors. First, as noted in other cancer types, the prevalence within endemic populations made differentiation difficult. Second, they are underrepresented in Lynch cohorts because of selection bias inherent in the use of Amsterdam Criteria and presence of CRC to determine study populations. Finally, deficits in our understanding of the nature and actual existence of other MMR mutations (MSH6) or non-MMR pathways, which are not even fully understood today, contribute to decreased knowledge of Lynch-associated hematologic malignancies.

As our understanding of the source mutations has improved, there have been numerous studies that would indirectly point to an association between hematopoietic malignancies and Lynch syndrome. In support of this, murine studies assessed the role of MSH6 in lymphoma proliferation and protection. The findings showed MSH2-deficient mice developed T-cell lymphomas, while MSH6-deficient mice developed B-cell lymphomas and leukemia. In the MSH6-deficient tumors, less than 50% of those lymphomas were found to be MSI-high, despite the known mutational events. Subsequent reasoning suggested both partially overlapping and independent functions of MSH6 and MSH3 in relation to PMS2 function. Intact MSH3 effects might in fact partially "mask" the effects of MSH6 deficiency, and may be a plausible explanation for the attenuated expression and phenotype. Similar reasoning was suggested by Lucci-Cordisco et al when studying atypical MSH6 presentation with both commonly seen Lynch-related malignancies and leukemias.^{45–47} This could also explain the low detection rate of clinical criteria, and the variability of Lynch syndrome phenotypes and tumor spectrums.

Based upon the aforementioned data, there is very likely a role for hematopoietic malignancies within Lynch syndrome that will continue to evolve, but presently will require a higher index of suspicion. Its potential role as an index or metachronous cancer within Lynch syndrome should not be overlooked.

Sarcoma

Sarcomas are rare and diverse malignancies when occurring sporadically in the general population. The peak ages at diagnosis vary somewhat based on location, but average between 60 to 70 years of age.⁴⁸ Familial sarcomas have been documented in conjunction with rare syndromes such as Li-Fraumeni syndrome, Werner syndrome, and neurofibromatosis I. Historically, sarcomas have not been included within Lynch syndrome phenotypes or clinical criteria. Over the last 10 to 15 years there have been increasing reports of sarcomas in Lynch syndrome cohorts, and findings of sarcomas harboring MMR mutations and MSI. These include malignant fibrous histiocytoma, osteosarcoma, leiomyosarcoma, liposarcoma, rhabdomyosarcoma, chondrosarcoma, and gliosarcoma.

Nilbert et al reviewed the incidence of sarcomas within the National Danish Registry. Collectively, the overall prevalence of sarcomas as extracolonic malignancies was 1%, which is also supported by numerous other studies.^{31,48,49} The average age at diagnosis was noted to be 43 years, 20 years earlier than sporadic sarcomas would be expected. The causative mutations were found to be MSH2 (50%), MLH1 (29%), and MSH6 (21%) among the sarcomas noted. This is also in line with other smaller reports that noted MSH2 as the causative mutation.

As with other discussed malignancies, the rarity of this tumor type makes it difficult to definitively associate with Lynch syndrome. However, sporadic sarcomas almost exclusively do not harbor MSI or MMR mutations as a driving force

in their development. Therefore the finding of sarcomas with MMR mutations and MSI gives credence to hereditary etiology.⁵⁰ This data represents mounting evidence that strongly suggests sarcoma should be considered an extracolonic Lynch syndrome cancer.

Interesting Index Cancers

My experience has revealed three specific instances of Lynch-proven patients with unexpected index cancers. All patients fulfilled AC II and revised Bethesda Criteria. The ages at diagnosis were noted to be 41, 46, and 60 years of age. The index cancers were (two) squamous cell carcinomas of the anal canal, and a rectal carcinoid. Tumor staining as well as germ-line testing confirmed MSH2 to be the causative mutation. Though these findings are clearly isolated and are viewed with caution, a literature search did not reveal any such malignancies having been reported in association with Lynch syndrome or as index cancers therein.

Summary

Our understanding of Lynch syndrome has evolved over time and continues to do so. The spectrum of extracolonic malignancies appears to be more diverse than once understood, and is very much different than the initial descriptions. In addition to well-documented malignancies, there is a growing list of other cancers that warrant inclusion in Lynch syndrome. At the same time, the role of extracolonic malignancies is evolving, as the index cancers may not be colorectal or other commonly seen cancers. Numerous factors determine the frequency of Lynch-associated cancers. These include geography, ethnicity, gender, and underlying genetic mutation. In addition, the responsible mutations and the diagnostic tools we use to define at risk individuals have changed. Although more MMR mutations have been recently identified, all mutations are not yet known. Finally, MMR mutations may not be the only pathway to Lynch syndrome, since the emergence of EpCAM, germ-line hypermethylation of MLH1, and possibly CHEK2. It is unclear if these genes also act in a comodulating role or in fact represent a separate Lynch-like syndrome. What is clear is that our index of suspicion must be higher. Population-based screening is needed to truly understand the incidence, phenotype, and scope of affected families. The role of extracolonic malignancies, within that screening, will be very prominent as the heterogeneity of expressed cancers becomes more evident.

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