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INVITED REVIEW ARTICLE

Current clinical topics of Lynch syndrome

Kohji Tanakaya[1]

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Abstract
Lynch syndrome (LS) is one of the most common genetic cancer syndromes, occurring at a rate of 1 per 250–1000 in the general population. This autosomal dominant disease is caused by a germline variant in one of the four mismatch repair genes, *MSH2, MLH1, MSH6, PMS2*, or the *EPCAM* gene. LS develops at early ages in colorectal cancer (CRC), endometrial cancer, and various other associated tumors. Accurate diagnosis of LS and utilization of various risk-reduction strategies such as surveillance, prophylactic surgery, and chemoprevention could improve clinical outcomes. The efficacy of surveillance has only been proven for CRC; however, specialists have proposed surveillance for other LS associated tumors. Universal screening for tumor tissue using microsatellite instability testing or the mismatch repair protein immunochemistry in all CRC or endometrial cancers is recommended not only as a diagnostic tool for LS, but also as a predictive, prognostic, and therapeutic marker. Next-generation sequencing methods have revealed several conditions with phenotypes similar to LS, such as Lynch-like syndrome, constitutional mismatch repair deficiency syndrome, and polymerase proofreading-associated polyposis. Distinguishing LS from these similar conditions is clinically important, since clinical management for patients differs according to the conditions. Recently, immune checkpoint inhibitors have been shown to be a promising treatment against mismatch repair-deficient (dMMR) solid tumors. The efficacy of immune-checkpoint inhibitors in LS-associated tumors has been shown to be similar to that in sporadic dMMR tumors. This review discusses current clinical topics related to LS screening, diagnosis, surveillance, and therapy.

Keywords Lynch syndrome · Mismatch repair · Universal screening · Multi gene panel testing · Immune-checkpoint inhibitors

Introduction

Lynch syndrome (LS) is one of the most common genetic cancer syndromes and tends to occur in the form of various types of tumors at a young age, such as colorectal cancer (CRC) and endometrial cancer. Aldred S Warthin, M.D. first reported LS in 1913 [1], while Henry T Lynch, M.D. contributed to the concept of genetic cancer syndromes [2]. LS has a population prevalence of approximately 1 in 250–1,000 individuals [3–6] and accounts for 1–4% of all CRC cases [7–9]. The number of patients with LS in Japan is estimated to be more than 100,000. Recent progress in genomic medicine has led to new approaches that could be useful for the management of LS. This review describes the current clinical knowledge related to LS screening, differential diagnosis, surveillance, and therapy.

✉ Kohji Tanakaya
tanakaya@iwakuni-nh.go.jp

[1] Department of Surgery, National Hospital Organization Iwakuni Clinical Center, Iwakuni, Japan

Clinical features

LS is an autosomal dominant disease caused by a pathogenic germline variant in a mismatch repair (MMR) gene. The causative genes are the four MMR genes *MSH2, MLH1, MSH6, PMS2*, and *EPCAM* [3, 4, 10]. *EPCAM* is upstream-adjacent to *MSH2*, and germline deletion of the 3′ end of *EPCAM* causes *MSH2* silencing via methylation of the *MSH2* promoter region [10]. The role of DNA MMR is to maintain genomic stability by correcting base mismatches and insertion–deletion mismatches that can arise during DNA replication. When the DNA MMR function is impaired, the sequence repeat number in simple repetitive sequences (microsatellites) is prone to changes. The altered number of repetitive sequences in microsatellites is termed

microsatellite instability (MSI). Thus, LS-associated tumors, with variants in MMR genes, commonly show a high frequency of MSI (MSI-H) [3, 11].

Carriers of MMR gene variants are at high risk of early-onset LS-associated tumors, which include CRC, endometrial cancer (EC), gastric cancer, ovarian cancer, pancreas cancer, renal pelvic/ureteral cancer, biliary tract cancer, brain tumors, sebaceous tumors, keratoacanthoma, and small intestinal cancer [12]. In *MSH2* and *MLH1* gene variant carriers, the cumulative cancer risk up to age 70 years is 30–82% for CRC and 14–60% for EC [13, 14]. The risk of gastric cancer is 6–13% in Western countries [13] and 24% for Japan (up to age 60 years) [15]. The cumulative cancer risk for CRC in *MSH6*/*PMS2* gene variant carriers is 10–22%, which is lower than that in *MSH2*/*MLH1* variant carriers [13, 14]. Furthermore, the cumulative cancer risk for EC in *MSH6* gene variant carriers is 16–71%, which is equivalent or higher than the risk for *MSH2*/*MLH1* gene variant carriers (14–60%) [13, 14]. In addition, the cumulative risk of urinary tract cancer in *MSH2*/*MLH1* gene variant carriers is high at 1–7% [13]. The tumor spectrum of LS has changed over time. The spectrum of LS in the family with LS first reported by Warthin included mainly gastric cancers and endometrial cancer [1]. However, follow-up reports of this family showed that in later generations, CRC was the most common tumor [2]. This change suggested that the cancer spectrum of LS is influenced by environmental factors, such as dietary and lifestyle habits, smoking, alcohol consumption, and obesity which interact with a host's genetic factors, and may modulate the risk of developing cancer. Due to the high frequency of death due to gastric and biliary tract cancer among patients with LS in Japan, management of gastric cancer and biliary tract cancer is as important as that of CRC and EC [16] (Table 1).

Diagnosis

Approach for diagnosis

Since CRC and EC are the most common LS-associated tumors and develop at earlier ages, their development often can be a clue for diagnoses of LS. Traditionally, as the first step for the diagnosis of LS, clinical criteria such as the Amsterdam criteria II (Table 2) [17] or revised Bethesda guidelines (Table 3) [12] had been used for selecting individuals for further testing. However, screening by using these criteria or guidelines could miss more than one-fourth of LS cases [7]. In 2009, therefore, the Evaluation of Genomic Applications in Practice and Prevention working group recommend screening all patients with CRC using either MSI testing or immunohistochemistry (IHC) [18]. IHC can be used, as a complement to MSI testing, to evaluate the expression of the MLH1, MSH2, MSH6, and PMS2 proteins in tumor tissues [3, 9]. In LS, 90% CRC show high-frequency MSI (MSI-H) or abnormality in IHC [3, 11].

Ten to fifteen percent of all CRCs show MSI-H in Western countries [3, 13, 14], whereas, in Japan, 6–7% show MSI-H [5, 19, 20]. Tumors that show MSI-H or abnormalities in IHC for MMR proteins are called deficient MMR (dMMR). Individuals with dMMR tumor are subjected to MMR gene testing. However, dMMR is not specific for LS. Presence of dMMR, in most cases, indicates epigenetic hypermethylation of the *MLH1* promoter region. To rule out sporadic MSI-H CRC, *BRAF* V600E testing can be used [3, 13, 14]. *BRAF* V600E somatic variant is observed in approximately 40% of sporadic MSI-H CRC cases [21, 22] but rarely in LS. IHC for BRAF protein expression (clone VE1) can also be used to rule out sporadic MSI-H CRC [23]. It is important to remember that the BRAF testing cannot be used for EC [24].

Nowadays, dMMR CRC screening is thought to be useful not only as a diagnostic tool for LS, but also as a predictive, prognostic, and therapeutic marker. [11, 25]; currently, many guidelines recommend universal screening for patients with CRC and/or EC [13, 14].

Given that, even universal screening would miss a small but significant minority (5–10%) of individuals with LS, and the frequency of the *de novo* variant in LS is low at 2.3% [26], it should be noted that recording family history is not reliable, but still an important complement to tumor testing. Additionally, because of the increased cost and heavy workloads for universal screening, genetic testing of relatives

Table 1 Amsterdam criteria I

At least three relatives must have a colorectal cancer; all the following criteria should be met
1. One must be a first-degree relative of the other two
2. At least two successive generations must be affected
3. At least one should have been diagnosed before the age 50 years
4. Familial adenomatous polyposis should be excluded
5. Tumor diagnosis should be confirmed by histopathological examination

Table 2 Amsterdam criteria II

At least three relatives must have a Lynch syndrome-associated cancer (colorectal, endometrial, small bowel, ureter, or renal pelvic cancer); all of the following criteria should be met:
1. One must be a first-degree relative of the other two
2. At least two successive generations must be affected
3. At least one should have been diagnosed before the age 50 years
4. Familial adenomatous polyposis should be excluded
5. Tumor diagnosis should be confirmed by histopathological examination

Table 3 The revised Bethesda guidelines for colorectal cancers for microsatellite instability testing

Tumors from patients with colorectal cancer (CRC) should be tested for MSI in the following situations:

1. CRC diagnosed in a patient less than 50 years old
2. Presence of synchronous, metachronous colorectal, or other Lynch syndrome (LS)-associated tumors,[a] regardless of the age
3. CRC with MSI-H histology[b] diagnosed in a patient less than 60 years old
4. CRC diagnosed in a patient with one or more first-degree relatives with a LS-associated tumor, with one of the cancers being diagnosed under the age of 50 years
5. CRC diagnosed in two or more first- or second-degree relatives with LS-associated tumors, regardless of the age

[a]LS-associated tumors include colorectal cancer, endometrial cancer, gastric cancer, small-intestinal cancer, ovarian cancer, pancreatic cancer, renal pelvic/ureteral cancer, biliary tract cancer, brain tumors, sebaceous gland adenomas, and keratoacanthomas

[b]Tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern

(known as cascade testing) is important for implementing the universal screening effectively.

Founder variants

More than 50 types of founder variants associated with LS have been reported worldwide [27]. In Japan, *MLH1* variant (exon5 c.381–431_c.453 + 717del1221) is considered a founder variant [28, 29]. Notably, a Japanese nationwide study conducted by the Japanese Society for Cancer of the Colon and Rectum reported that large deletion or duplication was common (26.6%) in Japanese patients with LS [30] including the *MLH1* founder variant. Therefore, if no pathological variant is detected using Sanger sequencing, the MLPA or other methods should be used to rule out large deletion or duplication.

Multi-gene panel testing

Conventionally, genetic testing is carried out in a stepwise manner; beginning with the most suspected gene, and if no genetic variant is detected, it proceeds to the second suspected gene. However, there are many types of tumors associated with LS, and phenotypes of LS overlap with a substantial number of other conditions and differential diagnoses. Therefore, stepwise genetic testing is too expensive and time consuming. With recent advances in NGS technology, multi-gene panel testing has been introduced since 2012 [31].

The benefits of multi-gene panel testing include: (1) high detection rate of pathologic variants, (2) cost-effectiveness, (3) suitability for sequencing a wide area of tumor suppressor genes in which hotspots are rare, and (4) clarification of the genotype-phenotype relations. Interestingly, the phenotypes for LS and *BRCA1/2*-associated hereditary breast and ovarian cancer syndrome have been shown to overlap. A study investigated individuals with suspected LS by multigene panel testing and identified 114 individuals with LS and 71 with variants in other cancer predisposition genes including 15 with *BRCA1* or *BRCA2* [32].

In contrast, the disadvantages of multi-gene panel testing include: (1) high detection rate of variants of uncertain significance, (2) lack of clinical management guidelines for moderate and low-penetrance genes, and (3) few standard genetic counseling models for multi-gene panel testing [33].

Differential diagnosis

There are many tumors associated with LS, and phenotypes of LS commonly overlap with other conditions. Typical differential diagnoses which show nonpolyposis colon cancer are as follows.

Constitutional mismatch repair deficiency (CMMRD) syndrome

CMMRD, also called biallelic MMR deficiency, is caused by homozygous or biallelic germline variants in MMR genes. During childhood, most patients develop CMMRD related tumors. Brain tumors are the most common, followed by CRC and hematological tumors [34]. Most patients have café au lait spots on their skin resembling neurofibromatosis 1 [35]. Gastrointestinal polyposis is observed in half of the patients [36]. In LS, variants of *MSH2* or *MLH1* are more common than *MSH6* or *PMS2*. In contrast, the most common MMR gene observed in CMMRD is *PMS2* followed by *MSH6, MLH1*, and *MSH2* [37]. Interestingly, a recent study reported that *MSH3*, which is one of MMR genes but has not been proven to cause LS, also causes CMMRD [38]. These findings suggested that biallelic variants of *MSH2* or *MLH1* might more likely to be embryonic lethal [39]. Currently, very intensive surveillance programs are proposed for CMMRD [39].

Sporadic MSI-H CRC

Epigenetic hypermethylation of the promoter region of the *MLH1* gene is the main cause of sporadic MSI-H CRC. The clinical features of sporadic MSI-H CRC include elderly

females, poorly differentiated adenocarcinoma, and right-sided colon preponderance. IHC shows absence of MLH1 protein expression. The somatic variant of *BRAF* V600E is observed in approximately 40% of sporadic MSI-H CRC [11], but rarely in LS.

Lynch-like syndrome

Patients with LS-associated tumors that show dMMR without hypermethylation of the *MLH1* promoter in the absence of a germline variant of MMR gene or *EPICAM* are termed to have "Lynch-like syndrome". Lynch-like syndrome is a heterogeneous condition and mainly caused by epigenetic bi-allelic variant of MMR genes [35, 40]. Lynch-like syndrome accounts for 18–71% of patients with dMMR LS-associated tumors without *MLH1* hypermethylation. CRC or EC in Lynch-like syndrome develops at earlier ages similar to LS. [5, 40, 41].

Familial CRC type X (FCCTX)

Families that meets Amsterdam criteria I (Table 1) [42], but who lack a germline variant in an MMR gene and an MSI-H tumor, are termed to have "familial CRC type X" [3, 43]. FCCTX is a heterogeneous condition. Candidates of causative gene include *BRCA2, SEMA4, NTS, RASSF9, GALNT12, KRAS, BRAF, APC, BMPR1A*, and *RPS20*, among others [44]. FCCTX accounts for approximately 40% of cases meeting Amsterdam criteria I. The onset age of CRC in FCCTX is 7.5 years more than that in LS, with the left-sided colon accounting for 70% of CRC cases. Histologically, this type is similar to sporadic CRC. The adenoma/carcinoma ratio is high and, the rate of development of cancer from adenoma is slow compared to LS [45, 46]. The risk of developing extracolonic LS-associated cancer is not increased in patients with FCCTX [15]. For surveillance of FCCTX, colonoscopy is conducted at intervals of 3–5 years, starting 5–10 years earlier than the earliest onset age of CRC in the family [45].

Polymerase proofreading-associated polyposis (PPAP)

PPAP is an autosomal dominant disease caused by germline variants in the proofreading (exonuclease) domains of DNA polymerases (DNA polymerase ε, POLE and DNA polymerase δ, POLD1) [47, 48]. Two hot spots of the gene variant have been reported (POLE p.Leu424Val and POLD1 p.Ser478Asn). Patients with germline *POLE* variants present oligo-adenomatous colorectal polyposis and CRC at an early age. Patients with germline *POLD1* variants present EC and brain tumor as well as oligo-adenomatous colorectal polyposis and CRC at an early age. Although PPAP associated tumors show stable microsatellites, these tumors are hypermutated or ultramutated due to loss of polymerase proofreading function [49]. Therefore, PPAP associated tumors might benefit from immune-checkpoint inhibitor therapy [50].

Surveillance

The efficacy of surveillance in LS has only been demonstrated for CRC; a 3-year endoscopic surveillance was reported to reduce mortality due to CRC by 65% [51]. However, because cancers can occur over the testing interval of 3 years, colon surveillance with endoscopy should be performed from 20 to 25 years of age at intervals of 1–2 years [3, 13, 14]. Because the progression from colon adenoma to cancer in patients with LS is faster than that in the general population, adenomas regardless of their size should be removed in patients with LS [11]. Gastric surveillance with endoscopy should be performed from 30 to 35 years of age at intervals of 1–2 years. The presence of *Helicobacter pylori* infection should be evaluated from approximately 25 years of age, and if detected, treatment should be performed [11, 52]. Small intestinal cancer is another LS-associated cancer, and when performing gastroscopy or colonoscopy, the duodenum and ileum should be observed whenever possible. Uterine/ovary surveillance with transvaginal ultrasound, endometrial biopsy/cytology, and serum CA125 should be conducted from an age of 30–35 years at an interval of 6 months to one year. Urinary tract surveillance with urine tests/cytology should be conducted from an age of 30–35 years at intervals of 1–2 years [3, 13, 14, 52].

Risk reduction surgery

Risk reduction surgery for CRC

An extended colectomy for CRC could reduce the risk of metachronous CRC. It also makes colonoscopic surveillance of the residual colon easier [53]. Therefore, extended surgery such as total colectomy or total proctocolectomy might be a good option. However, in clinical studies, extended surgery did not show better prognosis of CRC compared to partial colectomy, and might reduce bowel function. The US Multi-Society Task Force on colorectal cancer strongly recommended extended colectomy for patients with colon cancer in LS based on moderate evidence [14], however, a European group (Mallorca group) could only provide a weak recommendation, which was based on their expert opinion [52]. Thus, at present, no consensus has been reached on whether extended surgery is better management for patients with LS.

Table 4 Comparison of efficacy of immune checkpoint inhibitors against dMMR CRC with or without Lynch syndrome

Study	Drug(s)	Lynch syndrome			non-Lynch syndrome			
		n	ORR	DCR	n	ORR	DCR	p value
Le DT et al. [59]	Pembrolizumab	39	46%		32	59%		p = 0.27
Overman MJ et al. [60]	Nivolumab	27	33%	70%	28	29%	75%	
Overman MJ et al. [61]	Nivolumab + ipilimumab	35	71%	86%	31	48%	81%	

n subject number, *ORR* objective response rate, *DCR* disease control rate for ≥ 12 weeks

Risk reduction surgery for EC, and ovarian cancer

It has been reported that prophylactic hysterectomy and bilateral salpingo-oophorectomy can greatly reduce the risk of EC and ovarian cancer, respectively [54]. Especially, at the time of CRC surgery, these prophylactic surgeries have been considered to be a good option. Before making a decision, both patients and surgeons should take into account the stage of CRC, age of patients, their desire to have children, menopausal status, and gene variant type, among other factors [3, 13, 14]. Notably, a recent prospective study described a good prognosis for EC (98% 10-year crude survival) or ovarian cancer (89% 10-year crude survival) in patients with LS without prophylactic surgery [55].

Chemoprevention/drug therapy

Chemoprevention of CRC

The CAPP2 trial was a randomized controlled trial of LS variant carriers that evaluated the efficacy of aspirin (600 mg/day) on CRC, extra-colonic LS-associated tumors, and colon adenoma. Long-term aspirin use (at least 2 years) significantly lowered the risk of developing CRC and extra-colonic cancers [56]. Currently, CAPP3 trial is ongoing to study the optimal dose and administration period of aspirin.

Postoperative adjuvant chemotherapy for CRC

Postoperative adjuvant chemotherapy with 5-FU did not improve prognosis in Stage II colon cancer with MSI-H [57]. In contrast, postoperative adjuvant chemotherapy with oxaliplatin improved prognosis in Stage III colon cancer with MSI-H. However, only a few studies have been conducted with a focus on patients with LS.

Chemotherapy for advanced/metastatic CRC

MSI-H CRC is reported to be more common among stage II (~20%) than III (~12%), and less frequent in stage IV CRC (~4%) [58]. Efficacy of chemotherapy against metastatic dMMR CRC in patients with or without LS has not yet been clarified. Therefore, regimens for sporadic colorectal cancers are generally used for CRC in patients with LS.

Immune therapy for advanced or metastatic CRC (immune-checkpoint inhibitors) (Table 4)

The efficacy of immune-checkpoint inhibitors has been demonstrated against dMMR solid tumors. The US Food and Drug Administration (FDA) approved the use of checkpoint inhibitors in the treatment of dMMR solid tumors. PD-1 inhibitor monotherapies demonstrated no significant difference in the objective response rate for patients with or without LS: Pembrolizumab; 46 vs. 59%, and Nivolumab; 33% versus 29%, respectively [59, 60]. Combination immune therapy (Nivolumab plus Ipilimumab) demonstrated high response rates (55%) and disease control rate (80%) for ≥ 12 weeks [61].

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest to disclose.

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