Lynch Syndrome and Muir-Torre Syndrome: An update and review on the genetics, epidemiology, and management of two related disorders

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Abstract

Hereditary Nonpolyposis Colorectal Cancer (HNPCC), also known as Lynch Syndrome, is an autosomal dominant, tumor predisposing disorder usually caused by germline mutations in mismatch repair (MMR) genes. A subset of HNPCC, Muir-Torre Syndrome (MTS) also involves MMR gene defects and is generally accepted as a variant of HNPCC. MTS is typically characterized by at least one visceral malignancy and one cutaneous neoplasm of sebaceous differentiation, with or without keratoacanthomas. In either version of the disorder, nonfunctional MMR systems lead to the loss of genomic integrity, marked commonly by mismatches in repetitive DNA sequences, resulting in microsatellite instabilities. Deleterious nucleotide alterations ultimately drive the process of tumorigenesis in both HNPCC and MTS. The following article reviews the epidemiology, genetics, clinical presentation, and management of HNPCC and its MTS variant.

Keywords: autosomal dominant (AD), basal cell carcinoma (BCC), colorectal carcinoma (CRC), hereditary nonpolyposis colorectal cancer syndrome (HNPCC), immunehistochemical (IHC), interferon-alpha (IFN-α), Lynch syndrome (LS), microsatellite instability (MSI), mismatch repair (MMR), Muir-Torre syndrome (MTS)

Introduction

Muir-Torre Syndrome (MTS), first described in 1967 by Dr. E.G. Muir and one year later by Dr. Douglas Torre, has been recognized as a distinct variant of hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch Syndrome, with more than 200 cases reported worldwide [1, 2]. Another subtype of HNPCC is Turcot Syndrome, which is phenotypically distinct from MTS, presenting typically with gliomas/glioblastomas of the brain. HNPCC and MTS are inherited in an autosomal dominant pattern, although MTS can also arise sporadically as a result of acquired somatic mutations [1especially colorectal and endometrial tumors. The diagnosis of MTS relies largely on the microsatellite instability (MSI]. Turcot Syndrome is inherited in either an autosomal dominant or recessive pattern or perhaps both, with different sources citing different patterns of inheritance [2-5]. Common to all three disorders are genetic defects in the mismatch repair (MMR) system [6-8]. Altered MMR gene products fail to correct DNA replication errors, resulting in the expansion or contraction of small repetitive DNA sequences known as microsatellites [7, 9-11]. The consequent genomic alterations ultimately result in an oncogenic propensity, with typical MTS patients having at least one visceral malignancy and one cutaneous neoplasm of sebaceous differentiation, with or without keratoacanthomas [7, 8 , 12, 13]. In this article, we highlight the epidemiology, genetics, clinical presentation, and management of HNPCC and its variant, MTS.

Body of Article

Genetics and Epidemiology

According to a study by Chen et al., the population prevalence of HNPCC can be estimated at 1:440, with specific cancer risks depending on geographic and environmental factors [14]. Typically, HNPCC patients possess mutated MMR genes that result in DNA microsatellite instabilities, both of which can be tested for in resected tumors [15-17]. HNPCC patients have one functional MMR gene allele and one defective copy [17]. In 90% of cases, defects occur in the MLH1 (3p21) and MSH2 (2p16) genes; 7-10% of the time defects occur in the MSH6 (2p16) gene, and less than 5% of the time in the PMS2 (7p22) gene [18-20]. Malignant degeneration results once the second allelic copy becomes non-functional because of somatic mutations, or rarely because of methylation suppression [17, 21, 22]. The HNPCC phenotype can also be a consequence of germline deletions in the non-MMR gene EPCAM, which epigenetically silences the closely linked MSH2 gene [17].

Genotype-phenotype relationships are established, as cancer risk depends on the MMR gene mutated [18]. HNPCC patients with mutated MLH1 and MSH2 genes have significant DNA repair defects, and consequently, a higher oncogenic risk in comparison to patients with other MMR mutations, such as PMS2 and MSH6, who have low extracolonic cancer risks, though endometrial cancers are common [23-25]. Some studies report MSH2 patients to develop more extracolonic and multiple primary cancers and present less frequently with only colorectal cancer (CRC), as compared to MLH1 patients [26-29]. PMS2 mutations show the lowest risk for any HNPCC-related cancer [18]. Additionally, EPCAM mutation carriers show mosaic, cell-type specific inactivation of MSH2, and thus have a different tumor profile when compared to other mutation carriers [30, 31]. The risk for endometrial cancers in individuals with EPCAM deletions is significantly lower than those with mutated MMR genes [30, 31].

MTS is seen in 9.2% of individuals with HNPCC [32]. Most reported cases have occurred in Caucasian patients from developed countries; epidemiologic data in Asian and African populations is virtually unknown [31]. MTS is more frequent in men (male to female ratio 3 to 2) and the onset of malignancy ranges from 23 to 89 years with a median age of approximately 53 years [33]. Similar to HNPCC, a predominance of cases of MTS have a high penetrance with variable expression and have been traced to germline mutations in MSH2 and MLH1 genes, though a disease variant without MMR gene defects has also been described [17, 33-37]. Unlike HNPCC, 90% of MTS patients are reported to possess mutations in the MSH2 gene, with less than 10% harboring MLH1 defects [12, 19, 20, 32, 41-43]. Germline mutations in other mismatch repair genes are rare, cases of MTS with MSH6, PMS22 or MLH3 mutations have been reported [6, 12, 33, 36], (**Table 1**).

Sporadic cases of MTS have most commonly been

TABLE 1: *Genetic mutations associated with Muir-Torre Syndrome and Hereditary Nonpolyposis Colorectal Cancer [6,12,18,19,20,23-29,32,33,36,41-43]*

Gene	MTS	HNPCC
MLH1	<10%	50%; higher oncogenic risk
MSH2	90%;	~40%; higher risk for extracolonic cancers and lifetime risk of primary cancer development
MSH6	Less commonly reported	7-10%; higher risk of endometrial cancer development
PMS2	Less commonly reported	<5%; higher risk of endometrial cancer development; lowest risk of HNPCC-cancer development
MLH3	Less commonly reported	3%

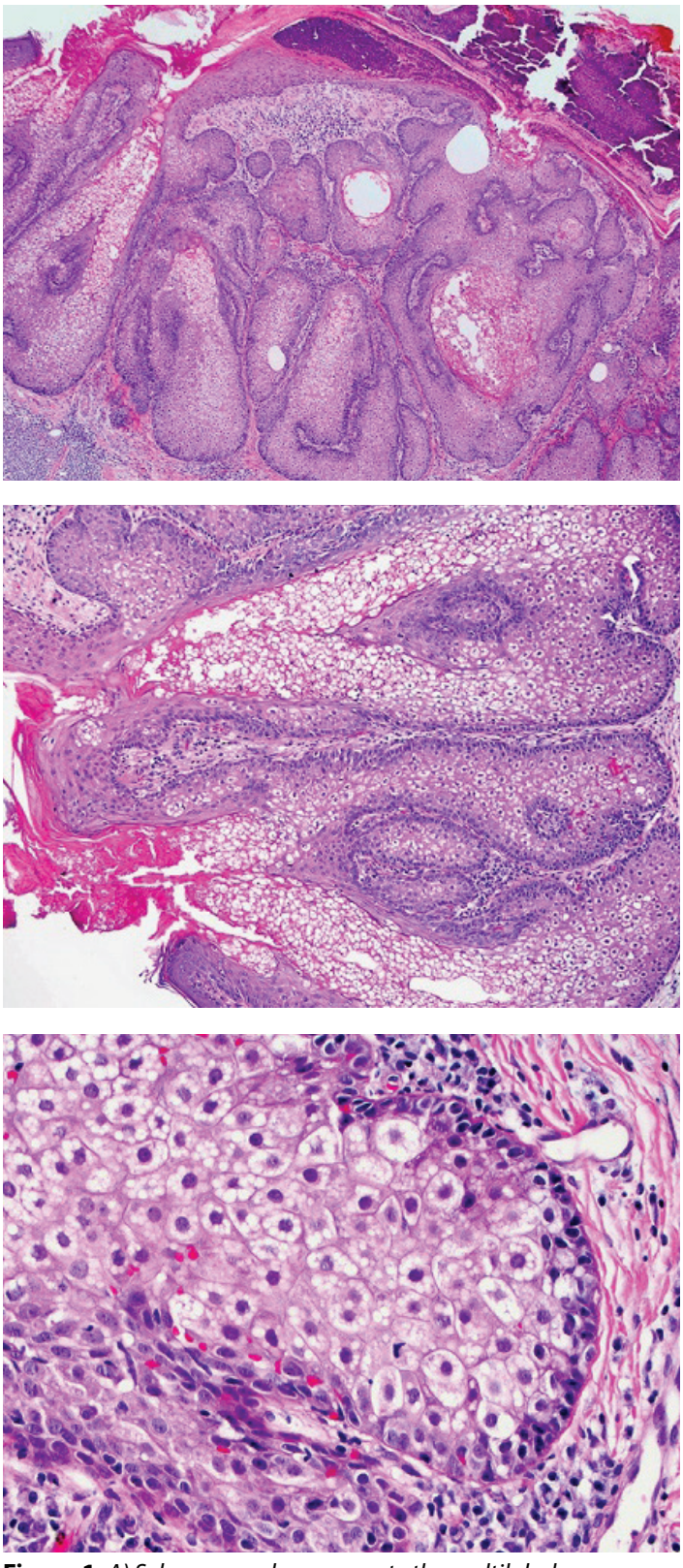


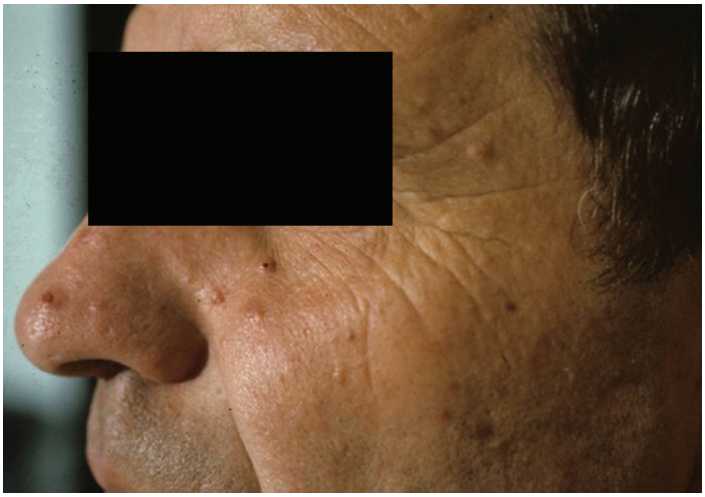
Figure 1: *A) Sebaceous adenoma; note the multilobular architecture (H&E, 4%). B) Magnification reveals a dark/basaloid component corresponding to generative cells, which are prominent at the periphery (H&E, 10%). C) There are ranges of cellularities present; the periphery contains germinative basaloid cells and the center consists of mature sebocytes with cytoplasmic lipid vacuoles (H&E, 40%). Images courtesy of Joshua Wisell MD and Francisco G. LaRosa MD, Department of Pathology, University of Colorado, Anschutz Medical Campus.*

documented in transplant and immunosuppressed patients [44]. Ultraviolet radiation, radiotherapy, and immunosuppression have been described to have possible effects on earlier tumor development in MTS patients [36]. Particular immunosuppressants, such as tacrolimus and cyclosporine, have been described to increase tumor proliferation [45, 46]. These medications promote tumor growth and invasion via increased levels of transforming growth factor beta and interleukin 6 [45, 46].

Clinical Presentations

HNPCC patients are very likely to develop multiple colonic adenomas, with CRC typically presenting at a mean age of 45 years [16]. CRC develops predominantly on the right colon and approximately 70% of patients are affected proximal to the splenic flexure [16-18, 47]. Based on a study by Win et al. [48], the cumulative risk of small intestinal cancer is increased more than 70-fold during the ten years following CRC development in HNPCC patients, as compared to the general population; for gastric and hepatobiliary cancers, the risk is increased 6-fold [48]. The second most common primary malignancy following CRC in both sexes with HNPCC is urinary tract cancer [16-18, 47, 48]. Mutation carriers are at an approximately 13-fold increased risk of developing malignancies in the kidney, renal pelvis, ureter, or urethra and have a 7-fold increased risk of developing urinary bladder cancer, as compared to the general population [48]. If we consider women only, however, then the second most common primary cancer is endometrial cancer [16-18, 47, 48]. In both males and females, hematopoietic, brain, bone, lung, and pancreatic malignancies may also be evident, but the rates at which these tumors are detected is not significantly higher than in the general population [48].

MTS is a rare disorder typically characterized by at least one internal malignancy and one sebaceous gland neoplasm, with possible keratoacanthomas [7, 8, 12, 13]. Sebaceous neoplasms are very rare in the general population and can be a clinical finding suggestive of MTS [36]. Spontaneous sebaceous tumors occur most commonly on the head and neck whereas sebaceous neoplasms inferior to the neck are associated with MTS [49]. Lesions present as yellow papules or nodules that may have central umbilication and ulceration



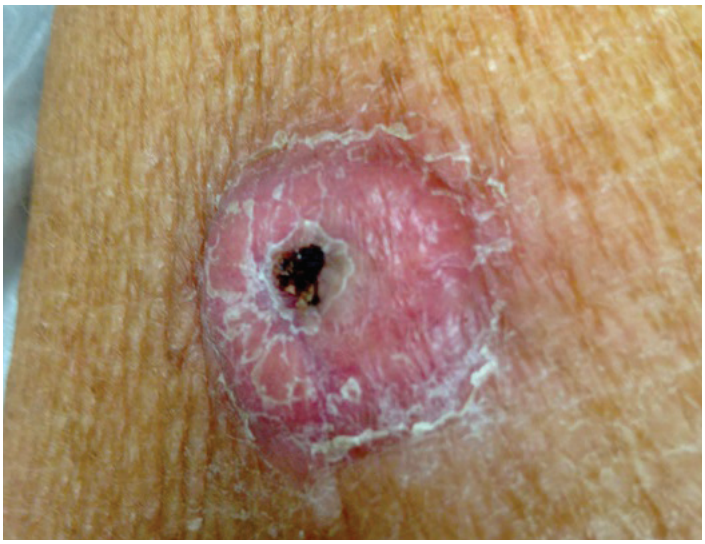


Figure 2: *Cutaneous neoplasms associated with the Muir-Torre variant of HNPCC. A) Multiple sebaceous adenomas on the face in a patient with MTS [31]. B) Keratoacanthoma; note the flesh colored, dome shaped lesion with a keratin and debris filled crater. Reprinted from Critical Reviews in Oncology/Hematology, 85 239-256, Giovanni Ponti a et al., Cancer-associated genodermatoses: Skin neoplasms as clues to hereditary tumor syndromes, Copyright 2013 with permission from Elsevier.*

and include sebaceomas, sebaceous adenomas/epitheliomas/carcinomas, basal cell epitheliomas with sebaceous differentiation, and seboacanthomas (**Figures 1, 2a**), [33,50]. These cutaneous neoplasms can present before, concurrently, or after the development of visceral malignancy, and typically follow a more indolent course as compared to their sporadic counterparts [51]. Sebaceous carcinomas, which are commonly misdiagnosed because of benign appearance, classically affect the periocular region and nose, though they can also involve the trunk and extremities in MTS patients [49, 50]. Sebomatricomas have been associated with MTS and can be an indicator for further investigation [52]. If keratoacanthomas (**Figures 2b, 3**) are present, they tend to occur in multiple groupings and appear on non-photodistributed areas of the body; they can present with or without sebaceous neoplasms in up to 20% of MTS patients [12, 53]. Findings of multiple keratoacathomas warrant further workup.

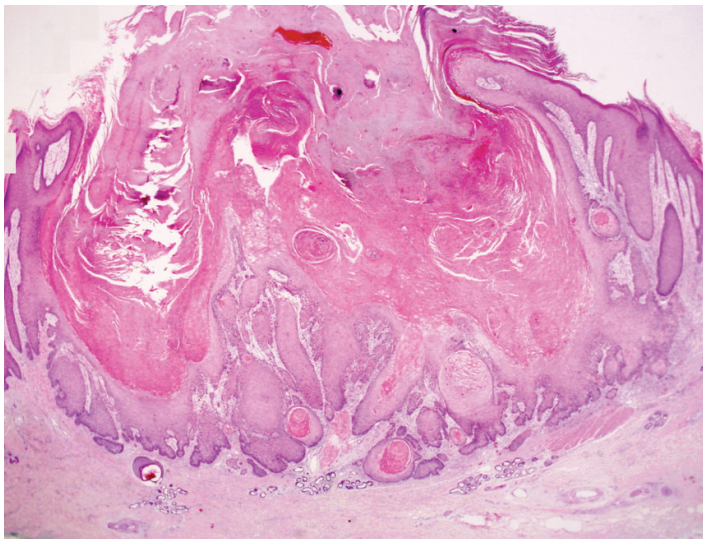


Figure 3: *Keratoacanthoma; note the hemispheric shape, keratin filled crater, overhanging edges, and irregularly infiltrating squamous nests and islands. The eosinophilic glassy appearance is the result of keratinization. (H&E, 2%).*

MTS has been described with several types of internal malignancy, with colorectal adenocarcinoma as the most commonly reported, presenting at an average of 50 years of age in MTS patients [54]. Other cancers include genitourinary, small bowel, breast, lung, and hepatobiliary [54]. Several cases of MTS patients developing central nervous system (CNS) tumors have emerged in recent years, with most cases developing years after colorectal carcinoma [55, 56]. It is interesting to note, all patients with CNS tumors were positive for MSH2 mutations, with maintenance of normal MLH-1, and had strong family histories of CNS malignancy [55, 56]. MTS patients may have a higher occurrence of CNS tumors possibly related to an overlap with another HNPCC variant, Turcot syndrome, in which patients present with CRC in addition to gliomas/glioblastomas of the brain [36].

Recommended Work-up

Diagnosis of HNPCC is most importantly made by a thorough clinical history of familial cancers [57]. Most hospitals currently perform immunohistochemical (IHC) staining for MMR gene products of all colorectal,

Table 2. *Revised Bethesda guidelines for testing colorectal tumors for microsatellite instability (MSI) [58].*

Tumors from individuals should be tested for MSI in the following scenarios:

- CRC diagnosed in a patient less than 50 years old
- Presence of synchronous, metachronous CRC or HNPCC-associated tumors, regardless of age
- CRC with changes in two or more of the five National Cancer Institute-recommended panels of microsatellite markers in a patient less than 60 years old
- CRC diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers diagnosed under age 50
- CRC diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age

TABLE 3: *Amsterdam II Criteria for the clinical diagnosis of HNPCC/Lynch Syndrome [45]*

At least three relatives must have a cancer associated with hereditary non-polyposis colorectal cancer (colorectal, endometrial, stomach, ovary, ureter or renal pelvis, brain, small-bowel)

- One must be a first-degree relative of the other two
- At least two successive generations must be affected
- At least one should be diagnosed before the age of 50 years
- Familial adenomatous polyposis should be excluded
- Tumors should be verified by pathological examination

small bowel, and endometrial cancers [44, 47]. If IHC staining is uninformative, additional studies should include microsatellite instability (MSI) profiling and/or direct analysis for specific germline mutations in MMR genes, though the testing sequence and recommendation to conduct these studies varies in the literature [44, 47]. The Bethesda guidelines (**Table 2**) are a widely used tool to help identify high-risk patients who should receive genetic testing. Specific tumors in which MSI should be tested for include: CRC found in a patient less than 50 years old; tumors in the presence of synchronous, metachronous CRC or HNPCC-associated tumors, regardless of patient age; CRC with changes in at least two National Cancer Institute-recommended panels of microsatellite markers in a patient less than 60 years old; tumors found in patients in whom CRC is diagnosed in one or more first-degree relatives with a HNPCC-related tumor, with one of the cancers diagnosed under age 50; and CRC found in a patient with two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age [58]. If a CRC BRAF mutation is detected during work-up, HNPCC can be essentially ruled out because activating mutations in BRAF are found in sporadic CRCs with MSI but are rare in HNPCC CRCs [59]. Commonly, clinical diagnosis of HNPCC is made using the Amsterdam Criteria (**Table 3**), [60]. If a patient is indeed diagnosed with HNPCC, he/she should be further evaluated for cutaneous tumors and first-degree relatives should be offered genetic testing to assess for HNPCC associated mutations [12].

Like HNPCC, diagnosis of typical MTS relies on a strong clinical history of familial cancers and the use of IHC, followed by either MSI profiling and/or mutational analysis of MMR genes. In a similar manner to the Bethesda guidelines, the Mayo MTS risk scoring algorithm (**Table 4**) may be used to identify patients who should undergo further germline MMR genetic testing [61]. IHC analysis of MSH2, MSH6, and MLH1 can provide additional useful information. Similar to patients diagnosed with HNPCC, MTS patients should be offered genetic testing and undergo annual evaluation for internal malignancy.

It has been recommended that all patients who present with a sebaceous neoplasm require additional work up, in which patients should be offered molecular genetic testing [53, 62, 63]. Initial tests should include an IHC analysis of MSH-2, MLH-1, and MSH-6. If unremarkable, MSI analysis should be pursued. In the case MSI analysis is negative but a patient has a positive family history, germline mutation analysis should be then considered. If

TABLE 4: *The Mayo Muire-Torre Syndrome Risk Score Algorithm.46*

Variable	Score
Age at sebaceous neoplasm[a] diagnosis (years)	
60 or older	0
Younger than 60	1
Total number of sebaceous neoplasms	
1	0
2 or more	2
Personal history of any Lynch-related cancer[b]	
No	0
Yes	1
Family history of any Lynch-related cancer[b]	
No	0
Yes	1

Total scores for each variable is summed to create the "Mayo MTS risk score," ranging from 0-5. A score of 2 or more has a sensitivity of 100% and specificity of 81% for predicting a germline mutation in a Lynch syndrome MMR gene.

[a]Mayo MTS risk score applicable to patients with sebaceous adenomas, sebaceous epitheliomas, sebaceomas, and sebaceous carcinomas

[b]Lynch-related cancers include CRC, endometrial, ovarian, small bowel, urinary tract, and biliary tract cancers.

both MSI analysis and family history are negative, no further work up is required. If MSI analysis is positive, the patient and family should consider routine cancer surveillance [53]. Thorough evaluation for visceral and neurological neoplasms may include upper and lower gastrointestinal endoscopy, genitourinary evaluation, chest and gastrointestinal imaging, cervical and urine cytology, fecal occult blood testing, and carcinoembryonic antigen levels [36, 43].

Solitary sebaceous adenomas are strongly associated with MTS and should warrant IHC and MSI gene analysis [36]. On rare occasions, if keratoacanthomas are evident without sebaceous tumors, a positive personal history of multiple visceral malignancies and a family history of MTS can also be diagnostic [64]. If Turcot Syndrome-HNPCC variant is suspected with MTS, a thorough evaluation for CNS neoplasms should be conducted as there have been recent reports of concomitant diagnosis of Turcot Syndrome and MTS, as well as reports of multiple of the HNPCC variants within a single family [65-67]. A complete neurological exam is recommended at the time of MTS diagnosis, and in young patients with multiple cutaneous neoplasms of sebaceous differentiation, with a low threshold for workup of CNS malignancy if neurological deficits develop [56].

Differential Diagnosis

Given HNPCC's noteworthy genotypic and phenotypic heterogeneity, the differential diagnosis for the syndrome is quite broad [19]. Although the differential diagnosis may vary depending on findings, they can include: Sporadic MSI-H colorectal adenocarcinoma, MUTYH-associated polyposis, serrated adenomatous polyposis, familial adenomatous polyposis (attenuated/classical/non-classical), hamartomatous polyp syndromes, hereditary diffuse gastric cancer, and BRCA1/BRCA2 hereditary breast/ovarian syndrome [18, 57].

Although sebaceous gland neoplasms and keratocanthomas can each be observed sporadically, there are a few non-MTS associated syndromes that should be considered in the differential diagnosis. In particular is autosomal recessive colorectal adenomatous polyposis, which occurs as a result of mutations in a base excision repair gene (MUTYH) and can present with CRCs, sebaceous adenomas/carcinomas, and other malignancies [50, 68].

Two further conditions include Ferguson-Smith syndrome, in which patients present with multiple self-healing keratocanthomas and Grzybowski syndrome, in which they present with generalized-eruptive keratocanthomas [50].

Management of Visceral Malignancy

HNPCC patients are recommended to have annual colonoscopies starting at 20-25 years of age [18]. In addition, they are also advised to undergo extracolonic screenings [18, 19, 47, 64, 69]. In women, assessment of the endometrium and ovary should be performed with an annual transvaginal ultrasound and endometrial aspiration for pathological assessment starting at the age of 30 years [19]. Screening of other sites, such as the upper uroepithelial tract and stomach, may also be considered, notably in native Korean or Japanese patients and in families with an excess number of extracolonic malignancies [18, 19]. Recently, a randomized controlled trial has shown aspirin to significantly reduce the emergence of HNPCC-related tumors, suggesting its therapeutic potential [70]. Prophylactic colectomy, total abdominal hysterectomy, and bilateral salpingo-oophorectomy are also options, though patient specific management must be established [19, 70].

Similarly, MTS patients are recommended to have annual cancer screenings. Annual colonoscopies can start as early as 18 years of age. Colorectal polyps and tumors should undergo MSI analysis, as they have a higher specificity and sensitivity for MTS in comparison to cutaneous tumors [61]. Women should undergo breast and pelvic exams annually. Individuals with positive genetic mutations are recommended to have additional yearly transvaginal ultrasound and endometrial sampling. Men are recommended to schedule annual testicular and prostate evaluation [36].

Management of Cutaneous Malignancy

Managing MTS is challenging because patients present with multiple, disfiguring sebaceous tumors and/or keratoacanthomas. It is advised that benign sebaceous neoplasms, including adenomas and epitheliomas, as well as keratoacanthomas be treated with conservative surgical excision or cryotherapy [69]. Although Mohs micrographic surgery followed by adjuvant radiotherapy has been noted to prevent the recurrence of sebaceous carcinomas in certain cases, wide excision with follow up for possible metastasis is the suggested management option [44, 69, 71, 72]. Radiation can be considered in complicated cases, such as recurrence, local metastasis, and palliative therapy [36]. In at least one case, recurrent metastatic sebaceous carcinoma has been successfully managed with 5-fluorouracil and cisplatin combination chemotherapy [71]. Oral isotretinoin, with or without interferon-alpha, has also been utilized to treat multiple keratoacanthomas; oral retinoid-interferon therapy is furthermore considered a useful chemoprophylaxis to prevent cutaneous tumor development [44, 69, 73].

Conclusion: HNPCC or Lynch Syndrome is a rare genetic disorder that carries an increased risk of CRC as well as other extracolonic cancers. Patients with MTS, a known and distinct variant of HNPCC, typically present with at least one visceral malignancy and one sebaceous neoplasm with or without keratoacanthomas. Although many of the pathogenetic details underlying HNPCC and MTS have been clarified over the years, it is still important to recognize the clinical overlap between the two syndromes, educate patients with a family history, and perform comprehensive clinical assessments, in order to provide better diagnostic and treatment outcomes for patients.

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Abbreviations

CNS: Central nervous system
CRC: Colorectal cancer
IHC: Immunohistochemical
HNPCC: Hereditary Nonpolyposis Colorectal Cancer
MMR: Mismatch repair
MTS: Muir-Torre Syndrome