Extracolonic Manifestations of Hereditary Colorectal Cancer Syndromes

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ABSTRACT

Familial colorectal adenocarcinoma (CRC) accounts for ~15 to 20% of CRC. Of these, hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP) represent the most common hereditary syndromes associated with CRC, followed by other less common diseases including juvenile polyposis (JP) and Peutz–Jeghers syndrome (PJS). Extracolonic manifestations are common in each of these syndromes having significant implications for surveillance and management in at-risk individuals. The authors review the most common and clinically relevant extracolonic manifestations for each of these syndromes focusing on incidence, presentation, genotype/phenotype correlations, and management (including surveillance) strategies.

KEYWORDS: Hereditary polyposis, colorectal cancer, extracolonic manifestations

Objectives: Upon completion of this manuscript, the reader should be able to recognize and manage the most common extracolonic manifestations associated to hereditary colorectal polyposis and cancer syndromes.

Familial colorectal cancer (CRC) accounts for ~15 to 20% of all CRC in the United States. These include patients with well-defined hereditary syndromes as well as those with clear familial association to cancer, but without a defined hereditary pattern.¹ Among those with hereditary syndromes, hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome represents ~2 to 3% of all CRC, followed by familial adenomatous polyposis (FAP) accounting for ~1% of CRC in the United States.² Other less common syndromes have been described including juvenile polyposis (JP), and Peutz–Jeghers syndrome (PJS). The specific genetic features involved in these syndromes have relevant implications for diagnosis, surveillance, and management of CRC in this population of patients as described in other sections of this issue.

Many of these hereditary syndromes can have extracolonic manifestations including the development of benign and malignant tumors. Although extracolonic manifestations are less common, they can be the first manifestation of an inherited syndrome as occurs with selected patients with HNPCC and, in many cases can be a leading cause of disease-related mortality as in patients with FAP. The rarity of these manifestations often limits our ability to guide management in these patients. However, an increasing understanding of the genetic mechanisms involved in each of these syndromes, the genotype/phenotype correlations and the information gained from large registry data has helped guide diagnostic, surveillance, and management strategies.^{1,2}

In this article, we will outline frequent and clinically relevant extracolonic manifestations of the most

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common CRC hereditary syndromes. We will focus on the indications for surveillance and diagnostic testing, genotype/phenotype correlations, as well as on current guidelines for management including prophylactic surgery, and how the presence of these extracolonic manifestations should be incorporated in decision-making strategies.

FAMILIAL ADENOMATOUS POLYPOSIS

FAP is a hereditary syndrome of autosomal dominant inheritance caused by a germline mutation in the adenomatous polyposis coli (*APC*) gene in chromosome 5. It is characterized by the presence of hundreds to thousands adenomatous polyps in the colon and rectum with progression to CRC if left untreated. Approximately 70 to 80% of affected individuals have a family history of FAP and 20 to 30% will present as new mutations.³ Typically, adenomatous polyps develop during the second decade of life and progress over time leading to CRC at a median age of 39 years.⁴

Both benign and malignant extracolonic manifestations are common in FAP patients. The most common extracolonic manifestations with FAP are upper gastrointestinal polyps, including gastroduodenal adenomas that can progress to cancer, and fundic gland polyps. Other less common extraintestinal malignancies include thyroid, brain, adrenal, hepatic (hepatoblastoma), and pancreatobiliary tumors. Benign tumors or lesions have also been described including desmoid tumors, lipomas, fibromas, sebaceous and epidermoid cysts, osteomas, dental abnormalities, and congenital hypertrophy of the retinal pigment epithelium (CHRPE), among others.⁵

As guidelines for surveillance and the indications and timing of prophylactic colectomy have been better defined, a reduced risk of CRC-related mortality has been achieved. Despite this, affected individuals have a

lower life expectancy than patients in the general population.⁶ Among FAP patients, the risk of death is higher than in the general population (3-fold); disease-related mortality is caused more commonly by upper gastrointestinal malignancies followed by desmoid tumors and perioperative complications.^{6,7} Hence, adequate surveillance and management of these lesions is essential. Similarly, presentation of extracolonic manifestations can help establish an early diagnosis of FAP in at-risk patients who have not yet developed colorectal polyposis.

Specific genotype/phenotype correlations in patients with FAP (Table 1) can guide management in circumstances in which no definite recommendations have been established.^{8–20} To date, only few genotype/phenotype correlations have been identified. In addition, there is no evidence-based data validating this approach and there may be inter- and intrafamilial variation among families and individuals carrying the same mutation.⁵

Upper Gastrointestinal Polyps

Upper gastrointestinal polyps in the setting of FAP are located in the stomach, duodenum, and periampullary region. Gastric polyps are typically nonadenomatous (~90%) benign fundic gland polyps. They develop in ~50% of FAP patients and are not associated with cancer. Gastric adenomatous polyps represent ~10% of gastric polyps, and when they occur, are most commonly located in the antrum.²¹ Adenomatous polyps can lead to gastric cancer. This progression is more commonly seen in Asian populations with FAP following the epidemiologic pattern of increased risk for gastric cancer in countries such as Japan and Korea. FAP patients in Asia have a 3-fold increased risk of developing gastric cancer as compared with well-matched controls, whereas FAP patients in the Western hemisphere do not appear

Table 1 Genotype/Phenotype Correlations of Extracolonic Manifestations in Patients with Familial Adenomatous Polyposis (FAP) and Attenuated FAP (aFAP)

Phenotype	Genotype	Comments
FAP		Multiple mutations described (> 400)
Desmoid tumors ^{9,11}	Beyond codon 1444	
Duodenal polyposis ^{28,34,35}	Exon 15, beyond codon 1400	
CHRPE ¹²	Exons 9–5	
Osteomas ¹⁹	Codons 767–1513	
Thyroid cancer ²⁰	Exons 1–15	
aFAP ^{13,14}	> 35 mutations described (exons 3, 4, 6, 9, and 15; introns 3 and 9)	No specific mutations reported to be associated with patterns of extracolonic manifestations Duodenal polyposis common Desmoids and other tumors are thought to be rare CHRPE not yet reported

CHRPE, congenital hypertrophy of the retinal pigment epithelium.

to have an increased risk of gastric cancer.^{22,23} No specific surveillance or management recommendations are outlined for patients with gastric polyps in the setting of FAP, except biopsy of fundic gland polyps for documentation. Adenomatous polyps should be removed. Due to the major implications of duodenal and periampullary polyps (see below), esophagogastroduodenoscopy (EGD) done for surveillance and management of these lesions serves as a surveillance tool for gastric disease as well.

Duodenal adenomatous polyps (DAPs) are common manifestations of FAP found in 30 to 70% of individuals with a lifetime risk approaching 100%.^{24,25} These polyps have a predilection for the second and third portion of the duodenum including the periampullary region. DAPs lag in time of presentation to colorectal adenomas by ~10 to 20 years with a median age of presentation at 38 years.²⁶ The implications of DAPs are related to development of advanced polyposis and invasive cancer. Patients with FAP have a 100- to 330-fold higher risk of developing duodenal cancer as compared with the general population²⁵ with an estimated cumulative risk of 4.5% by age 57 and a median age at presentation of 52 years.^{26,27} Others have reported an even higher cumulative risk of duodenal cancer of up to 10% by age 60.²⁸ Duodenal cancer is the second most common cause of disease-related mortality in patients with FAP surpassed only by advanced and metastatic CRC.^{6,7,29}

In an effort to standardize the management of DAPs in FAP patients, Spigelman and colleagues developed a classification system based on using the following prognostic variables: number, size, histology, and degree of dysplasia (Table 2).³⁰ A prospective study of patients with confirmed FAP from a five-nation registry demonstrated that 76% of patients with DAPs present with stages 0, I, and II, and 7% with stage IV DAP at the

time of first endoscopy. This study also demonstrated that the cumulative risk of advanced polyposis (stage IV) was 52% by age 70,²⁶ correlating with the known tendency for DAPs to progress over time with an estimated median time to progression between stages of 4 to 11 years.³¹ Similar results have been reported in other series.^{26,32} These findings are particularly relevant when considering the strong association between Spigelman stage IV polyposis and invasive duodenal cancer. After 10 years of follow-up, Groves et al reported a 36% incidence of duodenal cancer in Spigelman stage IV patients. Conversely, in that study none of the patients with stage 0 or I developed duodenal cancer during the follow-up period.³³ Although duodenal cancer was less common in the five-nation registry study (7% for stage IV DAP), the strong association between advanced polyposis and cancer was also seen in this study.²⁶

A genotype/phenotype correlation between mutations in exon 15—particularly those distal to codon 1400—and DAPs has been described.^{2,18,25,28,34,35} Increasing age appears to be correlated with a higher risk of progression to advanced polyposis.^{25,26,32} The presence of these factors, however, is not commonly used in the clinical setting in which standardized management guidelines have been proposed based primarily on the Spigelman's staging system and its association with risk of malignancy.^{2,5,21,25} Surveillance is recommended starting between age 25 to 30 or 5 years earlier than any affected family member with DAPs, whichever occurs first. The goal of surveillance (preferably with a side-viewing endoscope due to the high risk of adenomas in the periampullary region) is focused on identifying high-risk lesions that can be treated to avoid progression to cancer and early carcinomas amenable to surgical treatment. Endoscopic surveillance serves as a monitoring tool that allows identification of macroscopic disease and promotes random and directed

Table 2 Spigelman's Staging System for Duodenal Polyposis and Current Surveillance Recommendations

Variable	Scoring Criteria ³⁰		
	Points		
	1	2	3
Number of polyps	1–4	5–20	> 20
Size of polyps (mm)	1–4	5–10	> 10
Histology	Tubular	Tubulo-villous	Villous
Dysplasia	Low-grade		High-grade
Staging and Surveillance Recommendations^{2,5,21}			
Stage	Points	Surveillance Recommendations*	
0	0	Endoscopy every 4 years	
I	1–4	Endoscopy every 2–3 years	
II	5–6	Endoscopy every 2–3 years	
III	7–8	Endoscopy every 6–12 months Consider surgical consultation	
IV	9–12	Endoscopy every 6–12 months Surgical treatment indicated	

*Endoscopy with direct and side-viewing scope is advocated.

biopsy of suspicious lesions determining the presence of high-grade dysplasia.^{5,21}

In general, treatment options for DAPs include pharmacologic, endoscopic, and surgical treatment. Pharmacologic treatment, primarily with nonsteroidal antiinflammatory drugs (NSAIDs), is an option for patients with early disease, although its benefits have not been proven. Selected patients with diffuse polyposis not amenable to endoscopic treatment and who are not medically fit to undergo an operation may also benefit from these drugs.²¹ Endoscopic treatments include snare polypectomy, thermal ablations, and endoscopic mucosal resection. It should be noted that these procedures are associated with a risk of complications and have high recurrence rates reported between 50 to 100%.^{2,5,21} Endoscopic treatment has an important role in the management of focal lesions; it is also recommended for patients with high-grade dysplasia who are not thought to be good surgical candidates.² Surgical resection is indicated for patients with invasive cancer, those with Spigelman stage IV DAP, as well as for those with isolated features highly associated with coexistent malignancy or increased risk of progressing to cancer: size > 1 cm, high-grade dysplasia, villous architecture, and ulceration.² Surgical options for premalignant lesions include local excision approached through a duodenotomy, or radical resection including pancreas-sparing duodenectomy and pancreaticoduodenectomy. Radical resections are indicated also in patients with diagnosed invasive cancer.^{2,21}

Desmoid Tumors

Desmoid tumors (DTs) are slow-growing mesenchymal neoplasms composed of fibroblasts and myofibroblasts within a rich collagen matrix. They are characterized by the lack of metastatic potential, but exhibit an aggressive local behavior with infiltrative patterns of growth involving surrounding structures and a high local recurrence rate following resection. DTs are nearly 1000 times more common in FAP patients as compared with the general population and present in ~10% of patients with FAP.³⁶⁻⁴⁰ DTs are most commonly intraabdominal (~80%). Other sites include abdominal wall (~10 to 15%) and other extraabdominal locations (~5%).⁴¹ Although the natural history of DT is not well understood, intraabdominal DTs pose a challenge due to the common involvement of the small bowel and its vessels proximally. This can lead to significant small bowel resections resulting in short gut syndrome or alternatively, precluding the ability to achieve complete resections with subsequent high local recurrence rates (as high as 85%) and/or progressive local disease.^{42,43}

Although the exact etiology is unknown, it has been proposed that mesenteric DTs develop from abnormal fibroblast function causing mesenteric plaques, pro-

gressing to mesenteric fibromatosis and to DTs.^{44,45} Risk factors for the formation of DTs have been identified, and include surgical trauma; the majority of FAP patients with DTs have a history of previous surgery and tend to develop DTs within 5 years.^{36,40} Some FAP patients develop DTs prior to surgical interventions. The high female:male ratio, the observation of DT growth during pregnancy or while on oral contraceptives, and the response to antiestrogen therapy suggests hormonal association between estrogens and DTs.^{36,41} A family history of DTs (> 30% of affected family members) as well as the presence of osteomas is also associated with DTs.^{9,11,41} Patients with mutations toward the 3' end of the *APC* gene are more likely to have DTs; mutations beyond codon 1444 specifically, have been found to be independent predictors of DTs in patients with FAP.^{9,11,18}

Management of DT is complex and varies based on location, symptoms, extent of disease and pattern of growth. Although some lesions may remain stable for long periods, others exhibit rapid and relentless growth. In asymptomatic patients, a period of observation is advocated to establish the activity of specific lesions. Alternatively, the use of magnetic resonance imaging (MRI) may be helpful in predicting active growth when high-signal intensity is seen on the T2-weighted images.⁴⁶ Patients with abdominal wall or extraabdominal DT are usually imaged with MRI and can be managed surgically, assuming wide margins can be achieved.² Radiation therapy and medical treatment with NSAIDs, antiestrogens, and conventional chemotherapeutic agents are options, particularly when treating recurrent tumors.⁵

The management of intraabdominal DT is far more complex. In general, surgical treatment should be avoided unless unresponsive to medical treatment or if complications requiring emergent surgery occur. A staging system for intraabdominal DT was developed by the Collaborative Group of the Americas on Inherited Colorectal Cancer in an effort to optimize management through more defined guidelines.⁴¹ Stage I patients have small, asymptomatic, stable tumors, usually found incidentally during laparotomy or computed tomography (CT) evaluation for other reasons and are best managed with observation. Resection of a DT found at laparotomy is justified if easily resectable without risk to small bowel and other structures. Stage II DT are those measuring < 10 cm, symptomatic but stable. These tumors require timely treatment with resection if feasible or with NSAIDs (sulindac) and antiestrogens (tamoxifen or raloxifene) if thought to be unresectable. Stage III DTs are those measuring 11 to 20 cm and symptomatic or those asymptomatic but growing. Medical treatment is the mainstay of therapy using a combination of NSAIDs and antiestrogens initially. Other regimens including vinblastine/methotrexate or antisarcoma chemotherapy such as doxorubicin/dacarbazine alone or in combination

with other medications have been used, and are options when there is no response and/or continued growth while on other less toxic regimens.⁴⁷ Imatinib as an alternative in the management of aggressive desmoid fibromatosis has also been used.⁴⁸ Finally, stage IV DTs are those measuring > 20 cm, symptomatic, or those presenting with rapid growth or intraabdominal complications. These tumors are associated with a high rate of complications such as bowel perforation, bleeding, and sepsis and are generally the cause of desmoid-related mortality in FAP patients. Although surgery may be the only option in selected cases, it is often associated with a high risk of complications such as short gut syndrome.⁴¹

In patients with a high risk of developing DTs some authors have recommended delay of prophylactic colectomy when safe to do so.⁴⁹ When considering prophylactic surgery in these patients, total proctocolectomy with ileal pouch-anal anastomosis (IPAA) is advocated, if possible. This is associated with a lower incidence of DTs and minimizes future surgery if cancer or severe polyposis in the rectal stump after ileorectal anastomosis (IRA) develops.⁴⁰ In these cases, the development of DT after IRA may limit the ability to proceed with subsequent resection and IPAA, and may even preclude the possibility of adequate surgical treatment of a newly diagnosed rectal cancer.^{2,40}

Other Extraintestinal Malignancies

After CRC and duodenal carcinoma, thyroid cancer is the third most common malignancy associated with FAP. The lifetime risk of developing thyroid cancer is low and estimated to be ~2%. Typically thyroid cancer, which is most commonly of papillary histology, presents in the second and third decade of life. Some authors advocate an annual physical exam, with or without neck ultrasound, which should probably start at age 10 to 12.⁵⁰ The risk of pancreatic adenocarcinoma is also increased in patients with FAP with a lifetime risk of ~1.7%.⁵⁰ Similarly, hepatoblastoma is more commonly seen in this population of patients, affecting ~0.3% of children with FAP. Brain tumors, medulloblastoma in particular, have been associated with FAP and tend to present early in life. The incidence of these and other less common (adrenal, biliary tree, among others) extraintestinal malignancies is so low that the use of additional costly imaging studies is not currently recommended.^{2,5} However, surveillance tests should be considered in patients with strong family history of any of these specific extraintestinal manifestations and in those presenting with symptoms that could be attributed to these tumors.

Other Benign Tumors/Lesions

The presence of benign lesions associated with FAP can be useful in identifying asymptomatic mutation carriers

early during childhood. CHRPE are characterized by pigmentation of the retinal epithelium, which are generally bilateral and multiple in number. They occur in more than 90% of FAP patients, and can serve as a diagnostic tool for at-risk individuals.^{51,52} The implication of other less common lesions such as osteomas of the mandible (~80%), dental abnormalities (~17–75%), lipomas, and fibromas is less relevant except for helping in establishing phenotypic patterns of specific mutations.

Gardner's syndrome was first described in 1962.⁵³ This syndrome was characterized by the typical intestinal manifestations of FAP and the presence of osteomas, fibromas, and epidermoid cysts. However, after the discovery of the *APC* gene, others described additional extraintestinal manifestations in patients with Gardner's syndrome. Hence, the use of this term is discouraged because it refers to the different phenotypic expressions that can occur in patients with FAP, rather than to a specific phenotype.¹⁹

The colorectal phenotypic manifestations of FAP and the extracolonic manifestations may vary. Attenuated FAP (aFAP) is characterized by a milder phenotypic expression than its previously described classic form. Typically, fewer colorectal polyps (usually <100) and a higher predominance for the proximal colon are seen with onset of polyposis and progression to CRC occurring later in life.^{1,2} Multiple genotype/phenotype correlations have been reported in aFAP^{13,14} (Table 1). However, the variability of the phenotypic expressions in members of an affected family with the same specific mutation supports the idea that aFAP may be a range of disease within FAP-affected individuals rather than a completely different disease. The variability in phenotypic expression has limited the ability to establish a standardized definition of aFAP. It appears that the risk of upper gastrointestinal polyps and hepatoblastoma remains elevated, whereas other manifestations such as CHRPE, osteomas, and desmoid tumors are less prevalent.^{54,55} For patients with aFAP and extracolonic findings typical of FAP, surveillance and management strategies should follow the described recommendations for classic FAP.^{56,57}

It is difficult to determine the true incidence and characteristics of patients with MYH-associated polyposis. MYH-associated polyposis is a more recently described syndrome characterized by autosomal recessive inheritance. It is estimated to account for ~8% of patients with aFAP/FAP phenotype in whom no *APC* mutation is found. Some extracolonic manifestations have been described in patients with MYH-associated polyposis, such as duodenal polyposis, CHRPE, and breast cancer; however, these are less well characterized.⁵⁸

HEREDITARY NONPOLYPOSIS COLORECTAL CANCER

HNPCC or Lynch syndrome is an autosomal dominant syndrome characterized by early-onset CRC (median age of onset 45 years), right-sided predominance, increased risk of synchronous and metachronous tumors, and extraintestinal manifestations. It is caused by a mutation in one of the mismatch repair genes (MMR): *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Extracolonic manifestations include endometrial, gastric, urinary tract (renal pelvis and ureter), ovarian, small bowel, brain (glioblastoma and astrocytoma in particular), and sebaceous tumors. In general, CRC occurs in up to 80% of mutation carriers with extracolonic tumors occurring less frequently.^{1,2,59-61} Because there is not a classic phenotype as in FAP, establishing the diagnosis of HNPCC can be more difficult. A thorough personal and family history should be obtained. A family history of extracolonic malignancies can help identify a Lynch syndrome patient. Additionally, recognizing extracolonic manifestations in affected individuals is crucial in selecting patients for microsatellite testing or genetic testing. The Bethesda guidelines⁶² will help the clinician select patients for microsatellite testing and the Amsterdam criteria I and II⁶³ will help the clinician identify Lynch syndrome kindreds.

Endometrial Cancer

The cumulative risk of endometrial cancer in women with HNPCC ranges between 20 to 60%.⁶⁴⁻⁶⁶ Endometrial cancer occurs ~10 years earlier than in the general population with a mean age at diagnosis in the early to late 40s.⁶⁰ More importantly, endometrial cancer can present as the index cancer in up to 35% of women with HNPCC.^{64,66} Although no clear genotype/phenotype correlation has been noted in Lynch syndrome as in FAP, it has been reported that extracolonic tumors are more commonly associated with *MSH2* mutations. Families with mutations in *MSH6* have an increased risk of endometrial cancer, as well as later age onset of CRC as compared with families with *MLH1* and *MSH2* mutations.⁶⁷⁻⁶⁹

Current recommendations for surveillance start between ages 25 to 35, or 10 years before the earliest onset of endometrial cancer in affected relatives, whichever comes first.^{2,59} At least three studies have been reported where surveillance of at-risk subjects has led to the identification of endometrial cancer, usually at an early stage.⁷⁰⁻⁷² Therefore, screening is recommended every 1 to 2 years with transvaginal ultrasound combined with aspiration biopsy.^{2,72} Prophylactic total abdominal hysterectomy should be considered, particularly in the setting of high-risk patients (strong family history or *MSH6* mutation), in those undergoing prophylactic colectomy when childbearing is complete, or in post-

menopausal patients. In a retrospective study evaluating the impact of prophylactic hysterectomy on endometrial cancer risk, no endometrial cancer was found in 61 mutation carriers having prophylactic hysterectomy, whereas 33% of 210 affected patients in whom hysterectomy was not performed developed this malignancy.⁷³ Oophorectomy should also be considered at the time of hysterectomy, given the increased risk of ovarian cancer in patients with HNPCC (~10%),⁶⁴ its association with endometrial cancer, and the suboptimal results of screening methods for ovarian cancer (ultrasound and serum CA-125).⁵⁹

Other Tumors

It is difficult to establish guidelines for surveillance and management of less common HNPCC-associated tumors. The lifetime risk of other extracolonic malignancies is estimated to be ~10%.⁵⁹ For patients with a family history of gastric cancer and for those with a baseline higher risk than general populations (some Asian countries, for example), it is reasonable to consider surveillance gastroscopy every 1 to 2 years starting at age 30 to 35, although there is no strong data supporting its benefit. A similar approach should be used for patients with a strong family history of urinary tract cancers (renal pelvis and ureters) in whom surveillance with abdominal ultrasound, urinalysis, and urine cytology every 1 to 2 years starting also at age 25 to 35 may be beneficial. For other even less common tumors (brain, small bowel, etc.), no specific recommendations are outlined and early diagnosis should be based on a high index of suspicion, a complete family history, and thorough work-up when early symptoms appear.^{2,59,61}

OTHER POLYPOSIS SYNDROMES

Juvenile Polyposis

Juvenile polyposis (JP) is an autosomal dominant disease characterized by the presence of multiple hamartomatous polyps in the gastrointestinal tract, primarily the colon.⁷⁴ Its clinical diagnosis is based on the presence of hamartomatous polyps in the colon and rectum or diffusely distributed throughout the gastrointestinal tract with or without a positive family history of JP. JP has been linked to a mutation in either the *SMAD4* or the *BMPR1-A* genes, with each mutation being found in ~20% of JP cases.¹

Patients with JP usually present with rectal bleeding, abdominal pain, diarrhea, or anemia during the first two decades of life. A family history of JP can be elicited in 20 to 50% of patients.⁷⁵ Polyps are characterized by cystic dilation of the glandular type structures lined by normal-appearing epithelium.⁷⁴ This is particularly true for patients with *SMAD4* mutations, in whom a more

aggressive gastrointestinal phenotypic expression occurs both in the colon and rectum as well as in the upper gastrointestinal tract.⁷⁶ In addition, patients with JP are also known to be at increased risk of developing colorectal cancer.⁷⁷ Given the rarity of this disease, it is difficult to determine the incidence of other extracolonic malignancies. However, the cumulative lifetime risk of colorectal cancer has been reported to be 38%, and high rates of gastric (13.7%), duodenal (3.4%), and pancreatic cancer (3.4%) have been reported as well.^{77,78}

Surveillance strategies for patients diagnosed with JP focus on defining the extent of disease (polyposis) and identifying and removing polyps. Guidelines include baseline colonoscopy and upper endoscopy at age 15 or at the time of diagnosis, whichever comes first, and every 2 to 3 years thereafter. When polyps are found, surveillance endoscopy with polypectomy should be performed every year until clearance of polyps is achieved. There are currently no specific evidence-based recommendations for diagnosis or management of gastric, duodenal, or pancreatic disease. It is not uncommon however, to see patients with severe anemia due to continued bleeding from gastric polyposis, and in this case, subtotal or total gastrectomy can be considered.⁷⁷

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) is a rare disease affecting one in every 120,000 to 200,000 births.^{79,80} It is of autosomal dominant inheritance with variable penetrance and is characterized by hamartomatous polyps in the gastrointestinal tract and mucocutaneous pigmentation. Approximately 70% of individuals are found to have a germline mutation of the serine threonine kinase STK11/LKB1 gene with a wide range of reported rates of somatic mutations.¹ Hamartomatous polyps occur in ~90% of patients with PJS and are predominantly located in the small bowel and colon, although they have been reported to occur in the stomach and urinary tract too.⁸¹ Histologically they contain smooth muscle with a tree-like branching pattern and can measure 0.5 to 5 cm. Mucocutaneous lesions with increased pigmentation occur in close to 100% of patients with PJS and are due to increased melanocytes at the dermal-epidermal junction. These lesions are generally located in the lips, buccal mucosa, around the eyes and nostrils, hands, and feet. They appear early in infancy and with the exception of oral mucosal lesions, tend to fade during late adolescence or adulthood.⁸²

The clinical presentation of this syndrome varies from asymptomatic (individuals diagnosed after hyperpigmented lesions are identified early during childhood) to small bowel obstruction due to intussusception in children with small bowel polyps. Other symptoms include abdominal pain and rectal bleeding, as well as the development of gastrointestinal and extraintestinal

malignancies.^{82,83} Patients with PJS are at increased risk of developing breast, colorectal, pancreatic, small bowel, gastric, esophageal, uterine, ovarian, testicular, and lung cancers. A recent meta-analysis showed that patients with PJS have a 15.2 greater risk of developing cancer as compared with the general population, with a lifetime risk of developing cancer of 93%.⁸⁴ The same study revealed that the highest risk among PJS patients is of developing breast cancer (lifetime risk 54%), followed by colon and pancreatic cancer (lifetime risk 39% and 36%, respectively).⁸⁴ In another study evaluating the risk of cancer in 240 individuals with known mutation of the STK11 gene, it was reported that by age 70, 81% of patients had developed cancer and most of these cases were gastrointestinal in origin.⁸⁵

Most patients with PJS are diagnosed early in their 20s (median age 23 to 26 years),⁸² raising questions on how to carry out subsequent surveillance and management. No evidenced-based recommendations are available, and surveillance and management should be individualized for each patient.¹ However, there are published guidelines outlined by experts' opinions.^{5,82,86} Surveillance strategies are focused on identifying extensive or large-size polyps that could potentially lead to complications requiring emergent surgery, and early identification of the previously mentioned malignancies or precursor lesions. In affected individuals, a baseline upper endoscopy and small bowel series are recommended at age 8 to 10, and if positive every 2 to 3 years thereafter. If no abnormalities are seen, these can be deferred until age 18 and should be repeated every 2 to 3 years thereafter. Similarly, a baseline colonoscopy is recommended at age 18 and every 2 to 3 years thereafter. This strategy allows for early identification of malignant or precursor lesions and additionally (and perhaps more importantly), identifies patients at risk of developing acute gastrointestinal complications such as intussusception, small bowel obstruction, and/or bleeding. Polypectomy is advocated for patients with gastric or colon polyps > 1 cm, and for patients with small bowel polyps if symptomatic, rapidly growing, or ≥ 1.5 cm in size. When endoscopic removal is not feasible, surgery is indicated.^{5,82} An attempt to clear the small bowel of polyps—the “clean sweep” procedure—is advocated by some to reduce the need for subsequent laparotomies.⁸⁷

Surveillance for precursor lesions or early stage cancers starts at the time of birth in at-risk individuals. A complete personal and family history as well as a thorough physical examination focusing on testicular exam done annually until age 12 is recommended. In addition to the described surveillance tests for stomach, small bowel and colon, endoscopic ultrasound or CT scan and CA 19-9 (tumor marker test) of the pancreas is recommended at age 25 and every 1 to 2 years subsequently. For female patients, and due to the high risk of breast cancer, surveillance strategies similar to those for patients known

to have *BRCA1* or *BRCA2* mutations are recommended. These include monthly breast self-examination to start at age 18, with biannual clinical breast examination and annual mammography starting at age 25. Similarly, pelvic examination and Pap smear is advocated at age 21 and transvaginal ultrasound with serum CA-125 annually beginning at age 25.^{5,82,86}

CONCLUSIONS

Extracolonic manifestations in hereditary CRC syndromes are common and may be the first clue to the diagnosis of an inherited syndrome. Although often benign, malignant extracolonic manifestations may lead to the demise of the patient. Once a hereditary CRC syndrome is identified in an affected individual, surveillance must be performed in that individual as well as in at-risk family members.

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