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HAMARTOMATOUS POLYPOSIS SYNDROMES

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Abstract

Hamartomatous polyposis syndromes are a diverse group of inherited conditions grouped together because they exhibit hamartomatous rather than epithelial polyp histology. Each syndrome exhibits characteristic polyp histology, gastrointestinal polyp distribution, gastrointestinal cancer risks, extra-intestinal benign findings and often extra-intestinal cancer risks. Identifying individuals at risk for these syndromes and accurately defining the precise diagnosis is necessary for planning surveillance and management in order to prevent the benign and malignant complications. Characteristic syndrome features including gastrointestinal findings, pathology, genetics, and management options for the three most common hamartomatous polyposis syndromes, Peutz-Jeghers syndrome, PTEN hamartoma tumor syndrome, and juvenile polyposis will be presented in this review.

Keywords

hamartomatous polyps; Peutz-Jeghers syndrome; Cowden syndrome; juvenile polyposis; PTEN hamartoma tumor syndrome; STK11; SMAD4; BMPR1A; genetic counseling; genetic testing

Introduction

Hamartomatous polyps account for a small percentage of all colon polyps. These polyps arise from an over proliferation of subepithelial cells native to the tissue of origin, and can contain cellular components from any of the three germinal layers forming the intestines. The progression of hamartomas to cancer progression has not yet been fully delineated. It is clear

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however, that individuals with inherited hamartomatous polyposis syndromes have a greatly increased risk for malignancy. Kinzler and Vogelstein hypothesize that the risk for malignancy is due to defective “landscape” in which the environment created by the abnormal stromal tissue promotes the malignant progression of the adjacent epithelium [1].

Inherited syndromes predisposing to hamartomatous polyps occur less commonly than hereditary conditions leading to adenomatous polyposis, and account for <1% of all colorectal cancers [2]. While accounting for only a small portion of cancer, appropriate identification of families affected with these syndromes is crucial for planning screening and management. Hereditary hamartomatous polyposis syndromes are associated with high rates of malignancy and intensive cancer screening is necessary to maximize the opportunity for early detection. With this review we will present the clinical features, pathology, genetics, and management recommendations for Peutz-Jeghers syndrome (PJS), PTEN hamartoma tumor syndrome (PTHS), and juvenile polyposis syndrome (JPS).

Peutz-Jeghers Syndrome

Clinical Features

Peutz-Jeghers syndrome (PJS) occurs with an estimated frequency of 1/8,300 to 1/280,000 individuals [3], and is characterized by the development of mucocutaneous pigmentation, hamartomatous polyps throughout the digestive system, and an increased risk for malignancy of several types.

The characteristic pigmented macules present most commonly on the lips, buccal mucosa, and periorbital area, but they can also occur on the fingers, soles, palms, perianal area, labia, and intestinal mucosa [2-4]. These pigmented lesions are benign and not thought to have malignant potential. The pigmentation presents in infancy, but tends to fade during adolescence. However, pigmented areas inside the mouth or on the gums tend to persist into adulthood [4]. While greater than 90% of affected individuals will have characteristic pigmentation, the extent of the phenotype varies considerably from diffuse, dark freckling over the face to light pigmentation in characteristic areas (Figure 1) [5]. Reviewing childhood pictures and having patients remove cosmetics may be necessary to accurately assess the presence or absence of mucocutaneous pigmentation.

The median age for onset of gastrointestinal (GI) symptoms is 13 years of age, and approximately 50% will have experienced symptoms by age 20 [4,6]. Common presenting symptoms include small bowel intussusception and obstruction, rectal bleeding, and anemia. A small fraction of affected individuals will not develop symptoms until later in life or may only have vague symptoms such as abdominal pain [7,8]. In contrast to the other hamartomatous syndromes in which polyps occur most commonly in the colon, PJS related polyps occur most frequently in the small intestine. Over 90% of affected individuals will develop polyps in the small intestine during their lifetime. The incidence within the small intestine is greatest in the jejunum and progressively decreases in the ileum and duodenum. Up to 30% will develop polyps in the colon, and approximately 25% will develop gastric polyps [4]. Hamartomatous polyps may also develop outside of the digestive tract in the uterus, nasal cavity, bladder, and lungs [2].

A clinical diagnosis of PJS can be made when an individual has two or more of the following features [7]:

- 2 or more PJS polyps of the small intestine
- Characteristic pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
- Family history of PJS

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Individuals with PJS have an increased risk for numerous malignancies. The cumulative risk for developing any type of cancer has been estimated to be between 81%-93% [9-11]. Specific associated cancer risks are summarized in Table 1. The greatest specific cancer risk is female breast cancer (45%-54%) [9,10]. Approximately 57%-68% of affected individuals will develop some type of GI cancer [10,11]. While polyps occur most commonly in the small intestine, the colon is the most frequent site for GI malignancy. Sex cord tumors with annular tubules (SCTAT) of the ovary are a classic feature of PJS. Up to 36% of women who develop SCTAT have PJS [12]. Adenoma malignum, also called minimal deviation adenocarcinoma, is also characteristic PJS-related gynecological cancer [13]. Sertoli cell testicular tumors occur in males. These tumors pathologically resemble SCTAT tumors and often present prior to adolescence together with gynecomastia and accelerated physical growth [4].

Pathology

PJS polyps of the small intestine are characterized by a distinctive pattern of arborization of the muscularis mucosa. This feature is less prominent or absent from polyps occurring in other areas of the digestive system. During polyp development, some epithelial tissue may be involuted into the polyps, and these ectopic islands of epithelial tissue may suggest pseudocarcinoma invasion [4,14].

Genetics

PJS is caused by mutations in the STK11 (also called LKB1) gene located at 19p13.3. STK11 encodes a serine/threonine kinase which functions as a tumor suppressor. Mutations in this gene are detected in 50%-90% of individuals with PJS [6,15,16]. Variability in detection rates is likely due to differences in selection criteria and testing methodologies. The majority of mutations are truncating or missense mutations which eliminate the kinase function of the protein. However, up to 30% of mutations may be large deletions which would not be detected by sequencing alone [16]. Therefore the optimal approach for genetic testing of a proband would include both sequencing of the coding region of the gene and analysis for large deletions.

The likelihood of detecting a mutation is higher in individuals who meet the clinical diagnostic criteria compared to those who only have an isolated feature of PJS. Aretz et al. identified mutations in 53/56 (95%) of individuals meeting clinical criteria for PJS compared to 0/12 (0%) of those with only an isolated haratoma or pigmentation of the oral mucosa [16]. Other studies have likewise failed to find mutations in individuals exhibiting solitary features of PJS [6,17].

The addition of large deletion analysis to STK11 testing has greatly increased the mutation detection rate. However, there is still a very small portion of individuals and families meeting the clinical diagnostic criteria in which a deleterious mutation cannot be identified. It is possible that current methods are still missing mutations, and there are reports of families with a clinical diagnosis of PJS who do not link to 19p13.3 suggesting that there may be another genetic locus causing PJS in rare families [18]. At this time STK11 is the only genetic cause of PJS for which clinical testing is available.

In 2004 Amos et al. identified a significantly later age of onset of polyps and symptoms in individuals with missense mutations when compared to those with truncating mutations or no identifiable mutation (23, 13, and 15 years respectively) [6]. In the largest published series of individuals with PJS, Hearle et al. did not detect a significant difference in cancer risk based on mutation status or type [10]. Hearle et al. also recently looked at the relationship between mutation type and risk for intussusception, and found a trend towards earlier onset with truncating mutations, but the difference was not statistically significant [19]. At this time further studies are needed to determine if there is a relationship between genotype and

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phenotype. No distinctions in management should be made on the basis of mutation type or gene location. Mutations in the STK11 gene are inherited in an autosomal dominant manner. However, 25% of cases appear to be the first person affected in their family. Due to the variability of presentation, it is important to carefully evaluate first degree relatives for features of PJS before assuming an individual is affected due to a de novo mutation.

Management

Screening recommendation for PJS are outlined in Table 1. Managing polyps in the distal small intestine is particularly challenging. Capsule endoscopy (CE) has been found to detect more polyps than small bowel radiographic studies [20,21]. However, other studies have shown that CE still misses a significant portion of polyps. Soares et al. evaluated five patients having enteroscopy due to the finding of one or more large polyps with CE. During enteroscopy all of these patients had at least 20% or more additional polyps identified than had been seen with the CE screening alone [22]. Imaging with abdominal CT scan is another option for screening. A retrospective review of 165 Australian cases of small intestine tumors found that abdominal CT scans with oral contrast demonstrated greater sensitivity than small bowel radiography [23]. At this time there has not been a systematic trial comparing all these different methods. However, our center has been successfully using abdominal CT scan with oral contrast to screen PJS patients. Double-balloon enteroscopy unlikely has a role for routine screening, but may be used to remove polyps and reduce surgical procedures. Colonoscopy and upper endoscopy are recommended for screening the colon, stomach, and duodenum.

Approaches for pancreatic cancer screening include imaging with CT scan or magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS). EUS may be the most sensitive, but it is highly operator dependent [24]. Canto et al. have found intraductal papillary mucinous neoplasms (IMPNs) are a common finding in individuals at risk for familial pancreatic cancer or with a personal history of PJS. MRCP provides good visualization of the pancreatic ducts and cystic lesions and may be preferable to CT scan for screening these patients [25].

PTEN Hamartoma Tumor Syndrome

Germline mutations in the PTEN gene are responsible for a group of phenotypically diverse conditions, which have collectively been called the PTEN hamartoma tumor syndrome (PHTS). These rare autosomal dominant conditions include both Cowden syndrome (CS) and Bannayan-Riley Ruvalcaba syndrome (BRRS), which will be the focus here, in addition to possibly other seemingly unrelated disorders [26]. As the name implies, hamartomatous tumors, which can affect any organ, are the hallmark feature of the PHTS. CS is associated with a predisposition to benign lesions of the skin, mucousal membranes, GI tract and other organs, in addition to an increased risk of breast, thyroid and endometrial cancer. BRRS is a congenital disorder characterized by macrocephaly, lipomatosis, GI polyposis, and pigmented macules of the glans penis [27].

Cowden Syndrome

Cowden syndrome is the quintessential condition of the PHTS. It was first described by Lloyd and Dennis in 1963 and was named after their patient Rachel Cowden who presented with assorted benign findings and later died of breast cancer at age 30 years [28]. Although the prevalence of CS is currently unknown, it was once estimated to be as low as one in 1,000,000 [29]. The identification of the PTEN tumor suppressor gene in 1997 resulted in improved recognition of CS, which was made evident by updated prevalence estimates of 1 in 250,000 to 200,000 [29-31]. CS is likely still under diagnosed due to difficulties in recognition [32].

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Diagnostic Criteria

Consensus criteria have been developed to aid in the operational diagnosis of CS, which often presents with assorted manifestations [33,34]. The National Comprehensive Cancer Network (NCCN) Genetic/Familial High-Risk Assessment Panel (www.nccn.org) reviews the criteria on an annual basis and revisions have recently been published (Table 2). A clinical diagnosis occurs when individuals have any of the pathognomonic features or when specific combinations of the major and minor criteria are met (see Table 2).

The most important indicators of CS are mucocutaneous features, as they are found in nearly all individuals and are invariably present by the third decade of life [33,35]. Pathognomonic mucocutaneous features include trichilemmomas (flesh colored facial papules involving a hair follicle) which tend to occur around the mouth, nose and ears, papillomatous papules (histologically these are benign fibromas) which can result in a cobblestone appearance in the mucosal cavity, and acral keratoses (flesh colored or slightly pigmented smooth or verrucoid papules of the hands and feet) [33,36]. Adult onset Lhermitte-Duclos disease, also referred to as dysplastic gangliocytoma of the cerebellum, was recently added to the pathognomonic criteria for CS (www.nccn.org) [33]. Lhermitte-Duclos disease presenting in childhood is less often associated with CS compared to those presenting in adults, although young onset cases have been reported [37].

Additional Benign Findings

Other cutaneous features commonly seen in CS include lipomas, neuromas, hemangiomas and scrotal tongue [36]. Macrocephaly is present in approximately 40% of affected individuals [26]. Fibrocystic breast disease and breast adenomas (up to 75%), thyroid lesions including mulitnodular goiter and thyroid adenomas (up to 75%), and uterine leiomyomas (~50%) are additional benign lesions associated with CS, however, these features are also common in the general population and are therefore included in the minor criteria.

Gastrointestinal polyps

Hamartomatous polyps occur throughout the GI tract and were originally estimated to occur in 60% of affected individuals [35]. This is likely an underestimate, since GI polyps in CS are often asymptomatic and as few as 25% of reported cases have had their GI tract examined [38]. In a review of CS cases in Japan, the most common sites for GI polyps included stomach (75%), colon (66%), esophagus (66%) and duodenum (37%) [38]. Juvenile polyps are the most frequent lesion in the colon, stomach and small bowel, although multiple other types do occur, including lipomas, inflammatory polyps, ganglioneuromas, lymphoid hyperplasia, and adenomas [38,39]. The polyps in the esophagus are glycogenic acanthosis. These typically appear as white flat elevations, are numerous, and are spread throughout the esophagus (Figure 2) [39]. Although colon cancer has been reported in CS, it is still not clear whether this is part of the syndrome.

Associated malignancies

Although benign lesions are what usually prompt the identification of CS, breast, thyroid and endometrial cancers are included in the major criteria due to the increased risk associated with PTEN mutations (see Table 1 for associated malignancies). Women with CS have a 25%-50% lifetime risk for breast cancer, compared to a 10%-12% in the general population, and a 5%-10% risk for endometrial cancer, compare to less than a 3% risk in the general population [26]. Early onset malignancies are characteristic of CS with the average age of breast cancer onset occurring in the 40s [26]. Both men and women with CS have up to a 10% risk for non-medullary thyroid cancer; a female preponderance is seen. Renal cell carcinoma, melanoma,

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colon cancer and other cancers have been reported, however their association with CS is currently not known.

Bannayan-Riley-Ruvalcaba syndrome

In 1960 Riley and Smith described a mother and four children with macrocephaly and pseudopapilledema; two of these individuals also had hemangiomatas [24]. Bannayan in 1971 described a three year old with macrocephaly, lipomatosis, and angiomatosis [40]. A decade later Ruvalcaba and colleagues reported on two cases with macrocephaly, intestinal hamartomatous polypsosis, and pigmented macules of the glans penis [41]. Although originally believed to be distinct conditions, the cases described by Riley, Bannayan, Ruvalcaba, and colleagues are now believed to be part of the condition coined by Gorlin et al. in 1992 as Bannayan-Riley-Ruvalcaba syndrome (BRRS) [27]. BRRS is also known to be allelic to CS and is part of the phenotypic spectrum resulting from germline mutations in the PTEN gene [42,43]. Kindreds with both CS and BRRS have been reported [42-44].

No consensus criteria have been developed for the diagnosis of BRRS. It has been suggested that individuals having various combinations of macrocephaly, lipomatosis, hemangiomas, GI polyposis, and pigmented macules of the glans penis be considered clinically affected [34]. Mental retardation and assorted congenital abnormalities are also seen in BRRS [27]. In contrast to CS, GI polyps are frequently symptomatic in BRRS [45]. Breast, thyroid, and endometrial cancers are now also believed to be a component feature of BRRS [42,45].

Genetics

PTEN, also known as phosphatase and tensin homolog deleted on chromosome ten, is a tumor suppressor gene located on 10q22-q23. Germline mutations in PTEN are responsible for the PHTS. Mutations are detected in up to 80% of individuals with CS and 60% of individuals with BRRS [42,46]. The highest mutation detection rate has been found in families with both BRRS and CS [42]. It is estimated that 10%-50% of CS cases are familial [45]. Recently, it has been shown that approximately 20% of individuals with autism spectrum disorders and macrocephaly have germline PTEN mutations [47]. Previous studies have suggested possible genotype-phenotype correlations, however data supporting these relationships are lacking [44].

Genetic testing of PTEN is commercially available and is necessary in order to confirm the diagnosis of the PHTS. Predictive genetic testing should be offered to all at-risk relatives when a mutation has been identified in the family, even if a de novo mutation is suspected in the individual. A comprehensive evaluation for associated features in these at-risk relatives is imperative due to the heterogenous nature and variability in age of onset associated with PTEN mutations.

Management

Practice guidelines for the management of individuals with PTEN mutations have been proposed (www.nccn.org) and are reviewed on an annual basis at that site. Currently, screening recommendations are targeted to associated cancer risks (see Table 1). Due to the young average age of onset, earlier and more frequent breast cancer screening is recommended for affected women. For men and women, annual thyroid ultrasound starting at age 18 years should be considered. The optimal screening approach for endometrial cancer, renal cell carcinoma or other potentially associated cancers has not been resolved and participation in a clinical trial is recommended. Due to the high penetrance of multiple mucocutaneous lesions and previous reports of skin cancer (including melanoma) in CS, annual dermatologic exams should be considered for affected individuals. Since most individuals with PHTS will have GI polyps,

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baseline colonoscopy by at least age 40 and regularly thereafter, is recommended at some centers. However, further studies are needed to address the efficacy of earlier and more frequent colonoscopies, given that data are lacking supporting an association between germline PTEN mutations and increased risk for colorectal cancer.

Juvenile Polyposis

Clinical Features

Juvenile polyposis syndrome (JPS) is characterized by the development of multiple juvenile polyps in the GI tract [48,49]. An individual often presents with symptoms of JPS prior to age 20 [49].

Incidence

JPS occurs in approximately 1 in 100,000 individuals [2,50]. Of note, the appearance of singular juvenile polyps in children is not uncommon. This finding is present in approximately 2% of children and is believed to be fundamentally different from true JPS which involves multiple polyps [49,51]. Approximately 25%-50% of JPS cases are believed to be de novo – meaning the underlying genetic cause was not inherited from a parent, but could be passed on to children [14,51].

Clinical criteria

A clinical diagnosis of JPS is considered in anyone who meets at least one of the following criteria [52,53]:

- At least 3-5 juvenile polyps of the colon
- Multiple juvenile polyps found throughout the GI tract
- Any number of juvenile polyps in an individual with a family history of JPS

Pathology

Juvenile polyps are often reported out as inflammatory or hyperplastic, sometimes delaying the diagnosis of JPS [54]. True juvenile polyps are distinguished by inflammatory stromal tissue with mucus-filled cystic glands [48]. Smooth-muscle proliferation is not seen in juvenile polyps [49].

Genetics

Two primary genes have been associated with JPS to date: SMAD4 and BMPR1A. Both genes are part of the TGF-β signaling pathway. This pathway is highly involved in regulating the cell cycle, particularly in colonic cells [49]. Recent studies have shown that deletions in SMAD4 and BMPR1A, while less frequent than point mutations, account for a significant proportion of JPS-causing mutations [54-56]. Based on their data, adding deletion testing to SMAD4 and BMPR1A gene analysis will increase current standard mutation detection rates in individuals with clinical JPS.

Mutations in ENG and PTEN have been postulated to also account for a few cases of JPS. Due to the GI phenotype overlap between CS and JPS, individuals originally classified as having JPS with a PTEN mutation may truly have CS instead [49,55]. Out of a sample of 14 individuals clinically diagnosed with JPS and without identified SMAD4 or BMPR1A mutations, two mutations in ENG were identified [50]. ENG mutations are generally associated with a vascular genetic condition, hereditary hemorrhagic telangiectasia (HHT). Subsequent studies have questioned whether or not ENG mutations are causative of JPS. The contribution of ENG to JPS is still uncertain.

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Mutations in SMAD4 and BMPR1A are believed to account for approximately equal proportions of individuals with JPS (~20% each) [49]. However, some distinct genotype/phenotype correlations have been identified between these two mutation groups. Thus the phenotype of some individuals can assist with prioritizing genetic testing of one gene over the other. Given the polyp pathology overlap with CS, individuals with suspected JPS should be closely scrutinized for the additional extra-GI features of CS. PTEN testing could then be pursued in individuals who appear to have features suggestive of the PHTS [54].

Genotype/phenotype correlations

Genotype correlations have been found that can give assistance in predicting the timing and location of polyp development in JPS, as well as the likelihood of extra-GI manifestations in some instances. Since juvenile polyps can be seen in JPS and PHTS, phenotypic overlap occurs between the two [48]. Of note, BMPR1A is contiguous with PTEN on chromosome 10. Some individuals with partial or full deletions of both BMPR1A and PTEN have been described in the literature with varying phenotypic presentations [48]. Some of these individuals had phenotypes consistent with juvenile polyposis of infancy (JPI).

JPS Subtypes

JPI has been classified as a rare subtype of JPS typically presenting before age two [57]. JPI has a severe presentation and is frequently fatal. Infants with JPI can present with rectal bleeding, intussusception and/or diarrhea [48]. To date, JPI appears to be caused by de novo genetic mutations – no confirmed familial cases have been reported [57]. A 2006 study reported four unrelated individuals who all presented with JPI and were subsequently found to have contiguous deletions of BMPR1A and PTEN [57]. All four individuals had rectal bleeding prior to age two and were found to have colonic juvenile polyposis. One patient was found to have adenomatous polyps and foci of grade 3 dysplasia in the small intestine at age three, while another had adenocarcinoma in a duodenal polyp at age 14. Of interest, this latter patient was found to be mosaic for the BMPR1A/PTEN deletion. Three of the patients underwent colectomies at ages 10 months, 17 months, and 8 years. One of the children passed away at age three due to continued severe GI symptoms. All four of the children also had physical and cutaneous features consistent with PHTS, including macrocephaly.

A subsequent case report described a female patient with a de novo 12 MB interstitial deletion of the paternal chromosome 10, including BMPR1A and PTEN [58]. She did not present with symptomatic colonic juvenile polyposis until age five [58]. Interestingly, the macrocephaly and cutaneous features commonly associated with CS were not seen in this patient [58]. This phenotypic variability is further supported by a study of four additional individuals with BMPR1A/PTEN contiguous deletions where only one presented with GI symptoms prior to age two [48].

JPS-HHT

Symptoms consistent with HHT have been reported in individuals with JPS in multiple studies [14]. These symptoms include telangiectasia, epistaxis, and arteriovenous malformations (AVM's) (often located in the GI tract resulting in bleeding). Gallione et al. first reported individuals specifically with SMAD4 mutations with symptoms of both JPS and HHT and recommended they be reclassified as having a combined syndrome, JPS-HHT [59]. The presence of juvenile polyposis and anemia (due to AVMs) are the primary clinical features of this JPS subtype [60]. To date, the SMAD4 mutations in these individuals have all been located toward the 5' end of the gene (exons 8-11) [60]. HHT alone is most commonly caused by mutations in the ENG or ALK1 genes (60%-93%) [60]. In a recent study, 3 out of 30 unselected HHT patients (24 met clinical criteria, 6 likely had HHT), were found to have SMAD4 mutations [60].

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Gastric polyposis and SMAD4 mutations

In 2002, Friedl et al. identified a correlation between significant gastric polyposis (involving often large polyps) and individuals with JPS due to a SMAD4 mutation [61]. Out of the 7 unrelated JPS patients in their study group who had SMAD4 mutations, four of them had massive gastric polyposis (Figure 3) necessitating partial or total gastrectomy. This phenotypic difference remained consistent in examining the affected family members of the study group – individuals with SMAD4 mutations had much higher rates of gastric polyposis than BMPR1A mutation carriers and the gastric polyposis was much more severe. This finding has the distinction of being the first genotype/phenotype correlation identified in JPS. Of note, massive gastric polyposis is often complicated by GI bleeding and has a significant risk for gastric cancer.

Cancer risks

The primary cancer risks associated with JPS are confined to the GI tract: stomach, colon, and small intestine (see Table 1). The gastric cancer risk is predominately seen in individuals with JPS who develop multiple gastric polyps. As noted, the risk of gastric polyps in SMAD4 mutation carriers is much higher than what is seen in BMPR1A mutation carriers.

Management

Given the genotype/phenotype correlations delineated above, the management recommendations for individuals diagnosed with JPS can differ significantly (see Table 1). General endoscopy recommendations for individuals with JPS include colonoscopy and upper endoscopy starting at age 15, unless symptoms warrant earlier intervention [2,49]. This screening should be repeated annually if polyps are found, or every two to three years if no polyps are identified [2,49]. If the polyp burden in the colon and/or stomach cannot be managed with endoscopic removal, surgery is indicated (colectomy, gastrectomy, or small intestine resection) [49]. Multiple enterotomies with polypectomy and intraoperative enteroscopy with polypectomy are often performed for small bowel polyps to minimize loss of small bowel.

Individuals with JPS with an identified SMAD4 mutation should also have appropriate screening for AVMs consistent with published guidelines for HHT management [60,62]. If AVMs are detected, additional periodic imaging will be necessary to monitor the AVMs (particularly in the lungs to check for progression) [62]. Surgery may be needed to occlude the AVMs in order to prevent potentially life-threatening rupture.

Infants with JPS should be managed according to their symptoms [48,57]. No standard guidelines specific to the management of JPI have been issued, given the rarity of this condition.

Overall Genetic Evaluation and Testing for Hamartomous Polyposis Syndromes

For individuals with suspected hamartomatous polyposis, correct diagnoses hinge on multiple pieces of information. Review of medical records should include endoscopic/surgical reports detailing the number, location, and age of onset of the individual's polyps, plus the histologic type of these polyps and any cancers (GI or non-GI related). Reliable pathology reports on the removed/biopsied polyps are crucial. As discussed, hamartomatous polyps are not always reported as such in pathology reports [50]. While PJS polyps are distinctive, a pathologist who is unfamiliar with the features may not report them as PJS polyps. Having an individual's polyp slides reviewed by a GI pathologist can assist with proper polyp type identification and reduce diagnostic delays.

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The content of the individual's physical examination and questions regarding personal health history can both be tailored to focus on extra-GI manifestations of hamartomatous polyposis syndromes (i.e. macrocephaly, oral pigmentation, problems with bleeding, etc.). Elicitation of family history should be directed toward family members' GI polyp history, cancer diagnoses, and relevant extra-GI manifestations. By evaluating as much of this information as possible, a hamartomatous polyposis differential can typically be narrowed and genetic testing for one syndrome can be prioritized. If genetic testing cannot identify the causative mutation, the individual can be managed on the basis of his/her manifestations alone or by a working clinical diagnosis of a specific syndrome.

Summary

This review highlights the characteristics and management of the hamartomatous polyposis syndromes. These conditions represent a diverse group of inherited polyposis syndromes associated with high rates of benign and malignant complications, both gastro-intestinal and extra-intestinal. Appropriate diagnosis and treatment requires a team approach including medical and surgical specialists, genetic counselors, and pathologists. While the classic presentations of these syndromes allow them to be easily distinguished, many individuals present with features that overlap one or more of the conditions. Careful assessment of the phenotype, family history, and pathology is needed for clinical diagnosis and to determine the appropriate gene(s) to be assessed for genetic diagnosis. The initial identification of individuals with one of these syndromes most often occurs from endoscopic findings. But once a diagnosis is made multiple specialists are needed for management in view of the benign complications and cancer risks in and outside of the digestive system.

There are still many unanswered questions regarding the optimal management approaches. Many screening and surveillance recommendations are based on consensus rather than being evidence based. The development of chemopreventive agents, which would prevent or reduce the development of hamartomas and reduce cancer risk and the need for surgery would be of great benefit in this population. Several centers have established registries of families with these syndromes. Due to the rarity of these conditions, collaboration between multiple research registries is needed to better formulate management of the hamartomatous polyposis syndromes.

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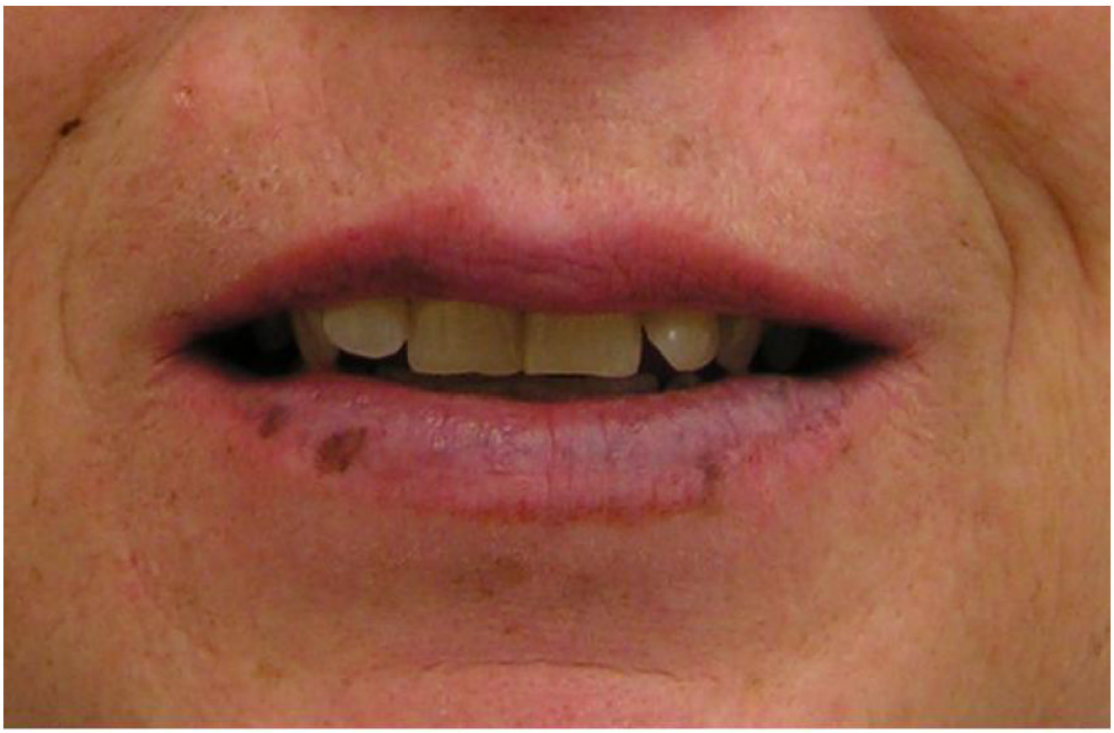

Figure 1.
Peutz-Jeghers associated pigmented macules

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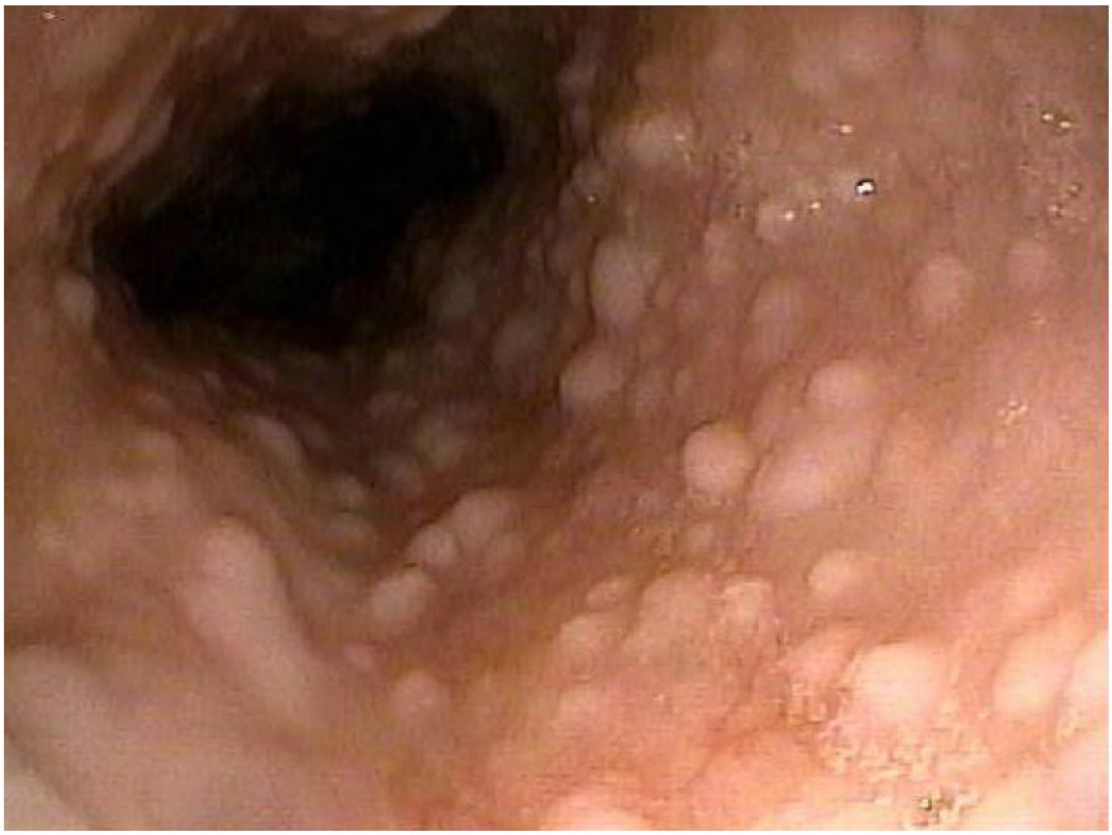

Figure 2.
Glyocogenic acanthosis associated with Cowden syndrome

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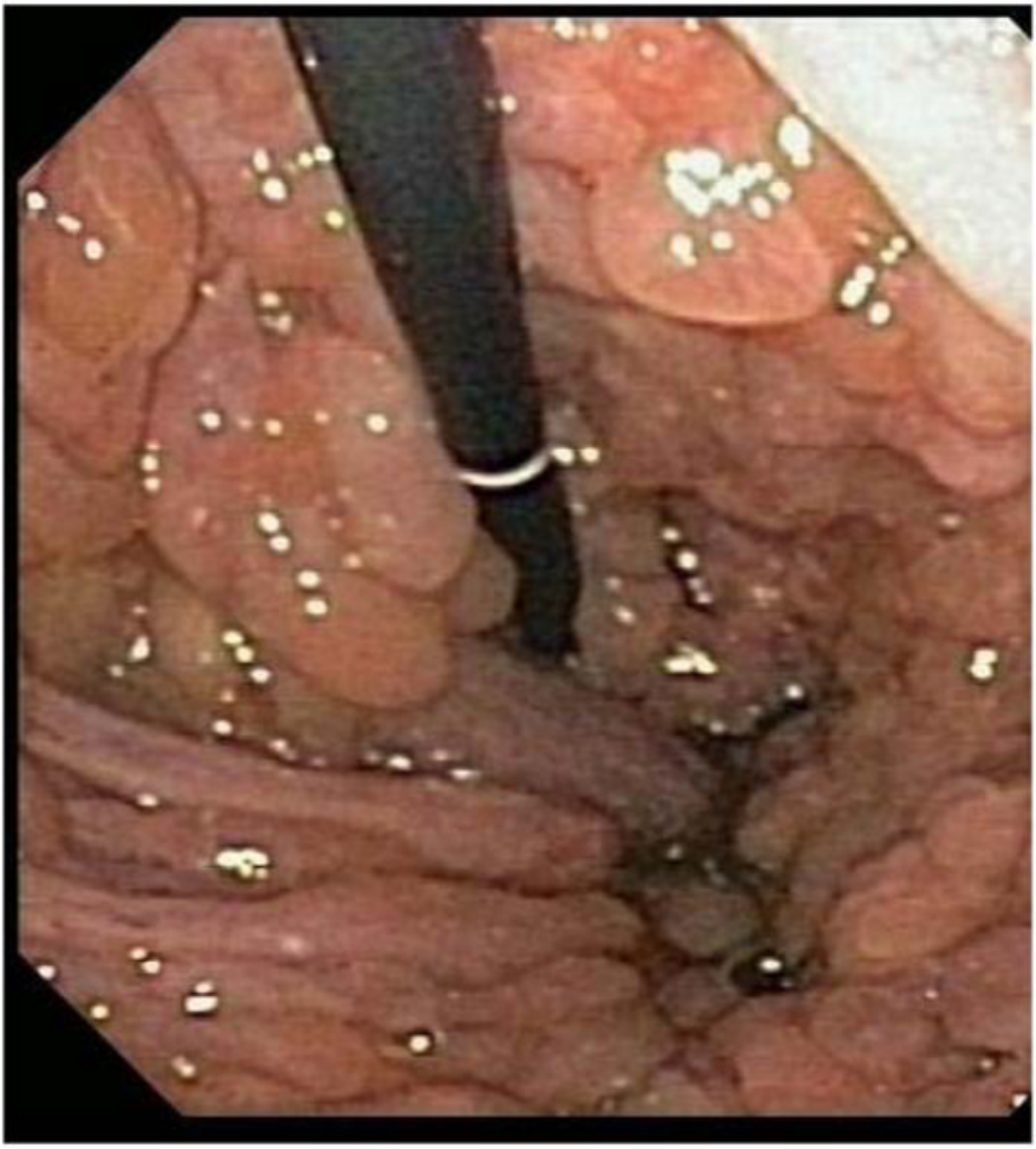

Figure 3.
Gastric polyposis in JPS due to SMAD4 mutation

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Table 1

Cancer risks associated with hamartomatous polyposis syndromes and management recommendations.

Syndrome	Cancer Risks		Cancer Specific Management Recommendations
Peutz-Jeghers Syndrome[4,9,10]	Breast	45%-50%	• Annual mammogram and breast MRI beginning by age 25 • Clinical breast exam every 6 months by age 25
	Colon	39%	• Colonoscopy every 2-3 years
	Pancreas	11%-36%	• Screening every 1-2 years with imaging of the pancreas with MRCP[a] and/or endoscopic ultrasound by age 30
	Stomach	29%	• Upper endoscopy every 2-3 years
	Ovary	18%-21%	• Annual pelvic examination and ultrasound by age 20
	Lung	15%-17%	• No specific screening recommend at this point • Provide education about symptoms and smoking cessation
	Small intestine	13%	• Upper endoscopy every 2-3 years and abdominal CT with oral contrast beginning at 10 years of age
	Cervix	10%	• Annual pelvic examination and Pap smear by age 18
	Uterus	9%	• Annual pelvic examination and ultrasound
	Testes	9%	• Annual testicular exam beginning at age 10 and observation for feminizing changes
Juvenile Polyposis	Colon	40%-50%	• Colonoscopy starting at age 15; repeat annually if polyps are found; if no polyps, repeat every 2-3 years.
	Stomach	21% (if multiple polyps)	• Upper endoscopy starting at age 15; repeat annually if polyps are found; if no polyps, repeat every 2-3 years.
	Small intestine	Rare, undefined	• No specific screening recommend at this point
	Pancreas	Rare, undefined	• No specific screening recommend at this point

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Syndrome	Cancer Risks		Cancer Specific Management Recommendations
PTEN Hamartoma Tumor Syndrome	Breast	25%-50%	• Annual mammogram and breast MRI by age 30-35 • Clinical breast exam every 6 months by age 25
	Thyroid (non-medullary)	10%	• Annual thyroid ultrasound by age 18 years • Annual physical exam by age 18 years with particular attention to thyroid exam
	Endometrium	5%-10%	• No specific recommendations at this point
	Skin	Undefined	• Consider annual dermatologic exam
	Colon + Kidney	Undefined	• No specific recommendations for increased surveillance

[a] magnetic resonance cholangiopancreatography

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Table 2

Diagnostic Criteria for Cowden Syndrome*

Pathognomonic Criteria

- Mucocutaneous lesions
  - Trichilemmomas, facial
  - Acral keratoses
  - Papillomatous papules
- Adult-Lhermitte-Duclos disease

Minor Criteria

- Gastrointestinal hamartomas
- Fibrocystic disease of the breast
- Lipomas
- Fibromas
- Genitourinary tumors (especially renal cell cancer) or structural malformations
- Benign thyroid lesions (eg, adenoma or multinodular goiter)
- Mental retardation (IQ ≤ 75)
- Uterine fibroids

Major Criterai

- Breast cancer
- Non-medullary thyroid cancer
- Macrocephaly (≥97th percentile)
- Endometrial cancer

Operational Diagnosis in an Individual

- Mucocutaneous lesions alone if:
  - There are at least 6 facial papules (at least 3 must be trichilemmomas), or
  - Cutaneous facial papules and oral mucosal papillomatosis, or
  - Oral mucosal papillomatosis and acral keratoses, or
  - At least 6 palmoplantar keratoses
- Two major criteria and one must be macrocephaly
- One major and three minor criteria
- Four minor criteria

Operational Diagnosis for Individuals with CS in the Family

- Pathognomonic criterion, or
- Any one major criterion with or without minor criteria, or
- Two minor criteria, or

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- History of Bannayan-Riley-Ruvalcaba syndrome

* Adapted from www.nccn.org