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Hamartomatous Polyps: Diagnosis, Surveillance, and Management.

Hamartomatous Polyps: Diagnosis, Surveillance, and Management.

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Abstract

Hereditary polyposis syndrome can be divided into three categories: adenomatous, serrated, and hamartomatous polyps. Hamartomatous polyps, malformations of normal tissue presenting in a disorganized manner, are characterized by an autosomal dominant inheritance pattern. These syndromes exhibit hamartomatous gastrointestinal polyps in conjunction to extra-intestinal manifestations, which require conscientious and diligent monitoring. Peutz-Jeghers syndrome, Cowden Syndrome, and Juvenile Polyposis Syndrome are the most common displays of Hamartomatous Polyposis Syndrome (HPS). Diagnosis can be pursued with molecular testing and endoscopic sampling. Early identification of these autosomal dominant pathologies allows to optimize malignancy surveillance, which help reduce morbidity and mortality in both the affected patient population as well as at-risk family members. Endoscopic surveillance is an important pillar of prognosis and monitoring, with many patients eventually requiring surgical intervention. In this review, we discuss the diagnosis, surveillance, and management of HPS.

Key Words: Hamartomatous Polyps; Peutz-Jegher Syndrome; Cowden Syndrome; Juvenile Polyposis Syndrome

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Core Tip: We hope that our review article, "Hamartomatous Polyps: Diagnosis, Surveillance, and Management", will function as a concise review of the literature as pertaining to the diagnosis, surveillance, and treatment of the most common Hamartomatous Polyp Syndromes.

INTRODUCTION

The national cancer institute defines a harmartoma as, "a benign growth made up of an abnormal mixture of cells and tissues normally found in the area of the body where the growth occurs" [1,2]. Diagnosis may be pursued based on personal or family history, endoscopic evaluation, and histopathology identified on endoscopic tissue sampling. The most common disease processes associated with hamartomatous polyps include Peutz – Jeghers Syndromes (PJS), Cowden Syndrome (CS), and Juvenile Polyposis Syndrome (JPS). While hamartomatous polyps themselves are benign, diligent surveillance is imperative as a significant risk of malignant transformation exists. Additionally, the disease process is often associated with an increased risk of other additional malignancies. As a result, management often requires multidisciplinary evaluation [1,3]. In this review, we discuss the diagnostic considerations, clinical manifestations, gastrointestinal (GI) and extra-intestinal surveillance recommendations, and management options of the most common syndromes associated with hamartomatous polyps.

PETUZ-JEGHERS SYNDROME

Diagnosis:

PJS is an autosomal dominant mutation of the mTOR pathway as a result of a germline mutation of the serine-threonine kinase (*STK11/LKB1*) tumor suppressor gene [4]. The *STK11/LKB1* gene is located on chromosome 19p13.3 and plays an important role in the secondary messenger pathway, which modulates cellular proliferation, responds to cellular energy deficits, and controls cellular polarity [5–7]. The incidence of PJS is estimated to range between approximately 1:8,300 and 1:200,000 with nearly 70% of cases demonstrating familial inherence and 30% of cases arising from a sporadic mutation [3,8,9]. Although there is often variable penetrance and clinical heterogeneity, diagnostic clinical criteria include: any number of polyps with a family history of PJS, two or more Peutz-Jeghers polyps (PJPs), mucocutaneous pigmentations with family history of PJS, or any number of PJPs with mucocutaneous pigmentation [4,8,10]. While endoscopically similar to other polyps, PJPs have a

characteristic phyllodes appearing epithelial component and a cystic glandular component which extends into the submucosa and muscular propria on hematoxylin and eosin staining [7,11–13]. Notably, PJPs are exclusively located within the small bowel. Gastric polyps associated with PJS have similar characteristics to hyperplastic gastric polyps and are not considered PJPs [7,12]. The median age of initial polyp development is 12 years-old, with nearly half of patients experiencing symptoms by the age of 20 [7,14]. The primary clinical manifestation of PJS is chronic bleeding from GI polyps leading to anemia. Small bowel obstruction secondary to an intussusception from a hamartomatous polyp of the GI tract occurs in up to 70% of patients, with the average age of diagnosis being 23 years-old [7]. Patients also characteristically present with mucocutaneous hyperpigmentations surrounding the oral cavity, eyes, nostrils, or surrounding the anus [15].

Surveillance:

Due the increased risk of gastrointestinal and extra-intestinal malignancies, a multidisciplinary approach to screening is encouraged. While the mean age of index cancer diagnosis is 41 years old, PJS is associated with an overall cumulated malignancy rate of 90% by the age of 70 [4,8]. GI malignancies commonly associated with PJS include gastric, intestinal, and the pancreatic. Additional extra-intestinal malignancy manifestations include breast, endometrial, ovarian, and lung [11]. Multiple studies have been pursued in order to further characterize the malignancy risk that is associated with PJS [Table 1]. The National Comprehensive Cancer Network (NCCN), European Hereditary Tumour Group (EHTG), and the American College of Gastroenterology (ACG) provide surveillance recommendations for patients [16–19]. A meticulous regimen of lifelong malignancy surveillance is imperative [Table 2].

Management:

Endoscopy is an essential modality of surveillance and management of polyps associated with PJS. Polypectomy during esophagogastroduodenoscopy (EGD) and

colonoscopy is particularly appropriate for patients with a limited number of polyps ranging from 0.5-1cm in size. If the polyposis that is encountered is too large or numerous to be managed endoscopically, surgical resection of the diseased segment may be pursued [18,27].

Management of small bowel polyps includes double balloon enteroscopy (DBE) or surgery. DBE allows for diagnosis and treatment of polyps located in the jejunum and the ileum. The device possesses a 200cm long etneroscope with a 145cm long overtube. There are two latex balloons attached to the tip of the endoscope and overtube, which are managed with a pressure-control pump system serving to prevent redundancy of the small bowel [28–30]. With this approach, manipulation and advancement of the scope may be occasionally impaired in patients who have previously undergone abdominal surgery secondary to intraabdominal adhesions, warranting intraoperative enteroscopy [31,32]. The European Society of Gastrointestinal Endoscopy (ESGE) recommends elective polypectomy for small bowel polyps that are >15-20mm in size to reduce the risk of intussusception. In symptomatic patients, polyps that are <15mm should be removed, as well [19]. Complications from DBE occur in less than <1% of cases, but include perforation, post-procedure hemorrhage, pancreatitis and aspiration [30,33]. DBE is an effective method for early detection and non-operative removal of polyps located in the small bowel [18,34]. Similar to polyposis of the colon, surgical resection may be required in the setting of numerous or large polyposis of the small bowel [19].

Surgical intervention is required for patients with PJS who present with intussusception, a phenomenon where the proximal segment of bowel telescopes into a distal segment of bowel with the polyp acting as a lead point. If no intervention is pursued, bowel ischemia and perforation may occur [4]. Patient with PJS possess a cumulative risk of intussusception reaching nearly 44% by the age of 10, which increases to nearly 50% by the age of 20 [35]. The risk of intussusception is greatest with polyps that are 15mm or larger [36]. Intraoperatively, frankly ischemic bowel evidently must be removed; however, polypectomy without bowel resection is recommended in

cases of reversible ischemia. As the risk of recurrent intussusception is present especially in younger patients, some authors have recommended further evaluate the bowel through manual palpation or enteroscopy *via* an intraoperative enterotomy in order to remove any additional polyps greater than 15mm [35,37].

According to the ESGE, pancreatic lesions should be addressed with partial pancreatectomies in the case of (1) solid lesions ^{3}10 mm unless known to be benign, or (2) IPMNs with high-risk features including mural nodules, enhanced solid component, obstructive symptoms, enhanced cyst wall, abrupt changes to duct size, and main pancreatic duct ^{3}10 mm [19,38].

Breast lesions should be managed based on current breast cancer guidelines, as no therapeutic strategy specific to PJS is presently available. A mastectomy for the purpose of risk reduction should be discussed in a multi-disciplinary setting accounting for additional patient risk factors and family history [19]. Similarly, while an established malignancy risk exists between PJS and cervical, uterine, and testicular cancer, no formal intervention guidelines specific to the correlation exists.

Studies have also demonstrated that the immunosuppressant agent Sirolimus (Rapamycin) has led to reduction in the number and size of polyps in a mouse model, which is largely attribute to the anti-angiogenic properties of the drug [39–41]. Currently, phase 4 prospective study for characterization of the drug in patients with PJS is being undertaken.

COWDEN SYNDROME:

***Diagnosis*:**

CS is an autosomal dominant mutation in the phosphatase and tensin homolog (*PTEN*) gene impacting the down regulation of the mammalian target of rapamycin (mTOR) pathway. Consequently, the *PTEN* regulation of cellular proliferation and survival is impaired [42,43]. The incidence of CS is estimated to be roughly 1:200,000 [44]. CS characteristically presents with hamartomatous polyps which may appear in any organ. Nearly all patients exhibit some type of skin lesion including

trichilemmomas, acral keratoses, and papillomatous papules. Additionally, nearly 80% of patient demonstrate gastrointestinal hamartomatous polyps and 80% of patients exhibit macrocephaly. Diagnosis is based on the guidelines established by the International Cowden Syndrome Consortium: patients must possess two major criteria one of which must be either macrocephaly or Lhermitte-Duclos disease (LDD), one major criteria with three minor criteria, or four minor criteria [Table 3] [45]. 40% of CS is associated with LDD - a rare, slow growing dysplastic gangliocytoma of the cerebellum manifesting with a broad range of clinical findings. The presentation of LDD may range from being asymptomatic to exhibiting signs of ataxia, cranial nerve palsy, vertigo, mental impairment and deterioration, intracranial hypertension, and hydrocephalus. The wide spectrum of clinical manifestations is attributable to the slow growing nature of the neoplasm [46,47].

***Surveillance*:**

The majority of patients with CS are at risk for developing breast, thyroid, renal, endometrial, colorectal, and skin malignancies [Table 4]. Given this established predisposition, attentive multidisciplinary surveillance and screening is an essential component of disease management [Table 5]. The purpose of these surveillance recommendations is early detection in order to allow curative oncologic treatment.

***Management*:**

There is no available curative treatment for CS. Rather, management is geared towards early detection of malignancy and timely oncologic treatment. Genetic counseling is also prudent in order to promote early detection and surveillance for kindred. Options for treatment of cutaneous lesions include, surgical excision, 5-Flurouracil (5-FU), carbon dioxide laser treatments, isotretinoin [54,55]. Polyps found on endoscopy may be removed endoscopically, if amenable. Otherwise, identified malignancies should be addressed utilizing the most up-to-date therapeutic regimens.

Associated Syndromes:

PTEN hamartoma tumor syndrome (PHTS) is a broad category of hamartomatous pathologies arising as pathogenic *PTEN* mutation variants identified by gene-targeted testing and comprehensive genomic testing. PHTS classically includes CS, Bannayan-Riley-Ruvalcaba Synromes (BRRS), PTEN-related Proteus Syndromes (PS), and *PTEN*-related Proteus-like syndromes (PLS). Notably, however, segmental overgrowth lipomatosis arteriovenous malformation epidermal nevus (SOLAMEN) syndrome also shares the same mutation [56,57]. It has been proposed that CS and BRRS may simply be varying spectrums of the same syndrome [58]. While formal diagnosis criteria are not present for BRRS, patients often present with macrocephaly, penile mucocutaneous lesions, delayed psychomotor development, and visceral hamartomas [58,59]. Approximately half of patients with BRRS have GI polyposis, with an analogous histopathologic presentation [58]. Nearly 60% of patients with BRRS possess a germline *PTEN* mutation [60]. SOLAMEN syndrome is also associated with hamartomatous polyps, macrocephaly, lipomas, and hemangiomas. These patients further possess an increased risk of skin, GI, thyroid, breast, brain, and genito-urinary malignant neoplasms [61,62]. Surveillance is advised to be similar to CS, given the mutual *PTEN* mutation association [Table 5]. Treatment is predominantly symptomatic, and often requires a multidisciplinary approach [63].

PS and PLS are similar pathologic process which may be associated with a *PTEN* mutations [64,65]. PS has been associated with *AKT1* and *PTEN* mutations, both of which influence the PI3KCA/AKT pathway [66]. Pulmonary embolism secondary to a hypercoagulable state and pneumonia are noted to be contributing factor to early mortality in this patient population. Other complications include scoliosis, CNS abnormalities, ophthalmogic complications, abnormal bone growth, and pulmonary malformations [67]. Treatment is often targeted towards correction of the functional limitations caused by the skeletal deformities associated with the disease. Patients should be closely monitored for the development of venous thrombosis; however, no recommendations for prophylactic anticoagulation currently exist [3,68]. Patients that

have presentations similar to PS, but do not possess all the diagnostic criteria are deemed to have PLS.

JUVENILE POLYPOSIS SYNDROME:

Diagnosis:

JPS is an autosomal dominant condition resulting from a germline mutation of the *SMAD4* or *BMPR1A* genes in 60% of the affected population. These genes impact the transforming growth factor-beta (TGF-beta) signaling pathway [69,70]. The estimated incidence of JPS is approximately between 1:100,000 to 1:160,000 [71,72]. Clinical diagnosis is based on the presence of one of the following: 5+ juvenile polyps in the colorectal region, 2+ juvenile polyps in the GI tract, or any number of juvenile polyps with a family history of juvenile polyposis [71,73–75]. Juvenile polyps refer to the histopathology of the polyps, rather than the age of onset. Juvenile polyps are hamartomas demonstrating a dense stroma with a smooth surface and mucin-filled cystic lamina propria [76]. Macroscopically, these pedunculated polyps have an erosive surface ranging from 5mm to 50mm in size. While distinction with sporadic juvenile polyps is difficult to make, JPS polyps frequently demonstrate epithelial neoplastic transformation, reduced stroma, reduced dilated glands, and increased proliferative glands [77].

Subtypes of JPS include JPS of infancy, generalized JPS, and juvenile polyposis coli. JPS of infancy is characterized by sessile or pedunculated polyps diffusely throughout the GI tract ranging from 1-30mm. Although further investigation must be pursued, some sources have reported JPS of infancy is caused by mutations resulting in the continuous deletion of *BMPR1A* and *PTEN* [78]. The disease process is plagued with early mortality secondary to the hemorrhage, malnutrition caused by diarrhea, and intussusception [77,79]. Considered to be a variable spectrum of penetrance of the same disease, generalized JPS occurs diffusely throughout the GI tract while juvenile polyposis coli is limited to the colorectal region [80]. Nearly half of patients with

generalized JPS or juvenile polyposis coli possess a heterozygous germline mutation of the *SMAD4* or *BMPR1A* gene [80].

Extra-intestinal manifestations are present in up to 15% of patients including midgut rotation, cardiac abnormalities, and craniofacial abnormalities. JPS may also be present in conjunction to hereditary hemorrhagic telangiectasia (HHT) syndrome [81,82]. Patients with HHT have a characteristic increased risk of bleeding secondary to greater rates of arteriovenous malformations of the lung, liver, brain, and GI tract. HHS is an autosomal dominant disorder also associated with a *SMAD4* gene mutation [81,83,84]. Patient may demonstrate varying degrees of disease qualities when they have both disorders simultaneously. However, the combination of both disorders results in a higher risk of colorectal malignant neoplasms and anemia [84,85]. Although further studies are required, the current perspective on the malignant pathogenesis of JPS includes the "landscaper mechanism" and the "gatekeeper" model. The "landscaper mechanism" postulates that genetic alterations lead to an abnormal stromal environment, which leads to malignant transformation of neighboring epithelium. A de novo study by Haramis *et al* demonstrated that bone morphogenetic protein (*BMP)*-4 inhibition, a common JPS pathway mutation, results in ectopic crypt units adjacent to the crypt-villus axis supporting the "landscaper mechanism" [86]. A "gatekeeper" model has also been proposed, where the biallelic *SMAD4* mutation contributes to malignant transformation and progression [87,88].

***Surveillance*:**

JPS has an established increased risk of GI malignancy, with a cumulative lifetime risk reported to range between 39%-63% [89,90]. The *SMAD4* gene has been associated with a greater risk of GI malignancies as well as a greater number of polyps in comparison to the *BMPR1A* mutation [69,91,92]. JPS is associated with an elevated risk of colorectal and gastric malignancies [Table 7]. Therefore, a combination of colonoscopy and EGD is recommended for appropriate screening and surveillance [93] [Table 8].

***Management*:**

Endoscopic management is typically feasible for patients with a limited number of polyps [18]. EGD may be utilized for surveillance and endoscopic removal of polyps located in the stomach and duodenum. In the setting of extensive polyposis, advanced dysplasia, or malignancy, a partial or complete gastrectomy may be pursued [98,99] Jaoude *et al* recommended proposed prophylactic gastrectomy in patients with symptomatic JPS, asymptomatic patients with a *SMAD4* mutation, or patients with unmanageable polyposis defined as >50-100 polyps[100]. Certainly, morbidity and mortality are greater with surgical intervention. However, surgical intervention must be weighed against the possibility of inadequate surveillance and treatment with endoscopy, particularly in the setting of an elevated likelihood for sporadic gastric malignancy associated with the *SMAD4* gene mutation. Further investigation should be pursued to determine the optimal parameters for surgical intervention, particularly in the prophylactic setting.

Small bowel polyps should be evaluated periodically with enteroscopy. Patient with limited small bowel polyps may be managed with endoscopic polypectomy but will require surgical treatment in the event of obstructive symptoms associated with intussusception. Colonoscopy is an essential screening and management tool for colonic polyps. However, in the setting of numerous polyps, advanced dysplasia, or malignancy, a colectomy may be pursued. Surgical options include protocolectomy with ileal pouch anal anastomosis (IPAA) or colectomy with ileorectal anastomosis (IRA) based on rectal involvement. Nearly half of patients who elect to undergo IRA will require additional proctocolectomy with IPAA secondary to the development of rectal polyposis [18,98,99].

An area of potential emerging investigation includes the utility of chemoprevention in patients with JPS. Van Hattem *et al* determined an increased expression of cyclooxygenase-2 (COX-2), particularly in patients with a *BMPR1A* gene mutation. Further investigation should be pursued in order to determine the clinical

implications of this expression profile [101]. Ultimately, additional studies should be pursued regarding the optimal management of these patients.

CONCLUSION

Hamartomas polyps result from hyperproliferations of normal tissues and are often associated with genetic mutations. While patients experience symptoms from the hamartomas themselves, there also exists an established malignancy risk associated with these disorders. Therefore, patient education regarding surveillance is imperative, and a multidisciplinary approach is often required for comprehensive management. First degree relatives should also be investigated for the diagnosis due to the dominant inheritance patterns that these disease processes possess. Due to the rarity of the disorders, limited studies are available on the clinical and molecular aspects of the disease processes, and further investigation should be dedicated to understanding the pathology associated with these syndromes.

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