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Endoscopic Management in Juvenile Polyposis, Peutz-Jeghers Syndrome, and Other Hamartomatous Polyposis Syndromes

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The hamartomatous polyposis syndromes constitute a group of at least six different rare diseases that may require endoscopic management. There are no prospective studies to prove the validity of any management approaches, but knowledge of the genetic basis and pathological manifestations of these diseases can be used to tailor approaches to intervention and surveillance in affected patients. Certain of these diseases have very high predispositions to cancer, which requires particular attention. The development of techniques to evaluate the small intestine and remove polyps nonsurgically has been of particular benefit for these patients.
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A modest proportion of colorectal cancers, perhaps 5%, are caused by germline mutations in genes that produce recognizable, syndromic diseases. The principal diseases in this category are Lynch syndrome (historically also called hereditary nonpolyposis colorectal cancer, or HNPCC) and familial adenomatous polyposis (FAP), which are discussed elsewhere in this issue. A less common, and more complicated, group of inherited intestinal cancer syndromes are the hamartomatous polyposis syndromes, which include Juvenile Polyposis, Bannayan-Riley-Ruvalcaba syndrome, Peutz-Jeghers syndrome, Cowden's disease, and a small number of very rare mixed polyposis syndromes in which one sees adenomas, hyperplastic polyps, and other lesions (Table 1). These syndromes are just now being deciphered at the genetic level,[1,2] but there are few good examples of evidence-based recommendations for their management at this time.[3-5] By virtue of more accurate classification in terms of the genetic basis of these inherited disorders, the true clinical manifestations are becoming clearer, and empiric measures are being applied on the basis of what seems reasonable in light of the risks for cancer, obstruction, bleeding, or other manifestations.

Most of the hamartomatous polyposis syndromes are caused by germline mutations in tumor suppressor genes, and as a consequence, the syndromes are associated with variable degrees of cancer risk. The nature of the genes responsible for these diseases was somewhat unexpected, since these polyposis syndromes do not give rise to primary neoplasms in the gut. It is easier to understand why FAP almost always progresses to cancer. The adenomas which characterize FAP are frank neoplasms, and the sheer number of them, together with the early age of onset, makes cancer an overwhelmingly likely consequence, given enough time. On the other hand, the hamartomatous polyposis syndromes are characterized by an overgrowth of cells or tissues native to the area in which they normally occur, and most of the polyps do not appear to be intrinsically neoplastic. The cells overrepresented in a hamartoma are typically derived from mesenchymal or stromal progenitors, although endodermal or ectodermal elements may also be involved. Importantly, virtually all of the hamartoma syndromes are associated with markedly increased lifetime risks of both intestinal and extraintestinal malignancies. It is important to recognize the clinical features of each of these diseases so that one can anticipate the cancers that are likely to occur, and manage the patients accordingly. Also, an understanding of the genetic bases of these diseases is essential for counseling the first degree relatives of affected patients, since this permits the appropriate use of surveillance measures, and equally as important, those relatives who do not carry the gene responsible for the disease can be spared inappropriate and unnecessary procedures.

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Table 1 The Hamartomatous Polyposis Syndromes

Syndrome	Population Frequency	Gene(s) Involved
Juvenile Polyposis Syndrome	1/100,000	*BMPR1A* or *SMAD-4*
Bannayan-Riley-Ruvalcaba Syndrome	? (very rare)	*PTEN*
Cowden's Disease	1/200,000	PTEN
Peutz-Jeghers Syndrome	1/70–200,000	*STK11* (*LKB1*)
Hereditary Mixed Polyposis Syndrome	5 known kindreds	*CRAC1* on 15q (?)
Hyperplastic Polyposis	Unknown	Unknown

Juvenile Polyposis Syndrome (JPS)

Clinical Features

Juvenile polyps are distinctive pathological lesions that occur as solitary rectal polyps in 1% to 2% of children. They have a smooth surface covered by normal colonic epithelium, and the lamina propria is edematous and contains inflammatory cells (Fig. 1). The pathological appearance of these polyps has given rise to the occasional term, retention polyp, and the inflammatory infiltrate can prompt the pathologist to give additional descriptions and names to these lesions, when they occur in isolation.

JPS is a rare autosomal dominant entity in which the patient develops multiple juvenile polyps. Traditionally, more than 10 juvenile polyps indicates juvenile polyposis, but more than 5 should raise suspicion for this disease. Some patients have predominant colonic involvement, but others can have involvement proximally in the gut, and these can be particularly problematic in some patients. JPS patients are usually diagnosed by age 30, but the mean age of presentation is 9.5 years. The diagnosis is reached on the basis of the pathological features of the polyps. This syndrome may be suspected clinically, in part, by exclusion of the extraintestinal (usually cutaneous) manifestations seen with the other hamartomatous syndromes.

An estimate for prevalence in the population is 1 in 100,000 individuals. JPS patients often present with rectal bleeding, but with a large number of small intestinal polyps, patients can present with protein-losing enteropathy, malnutrition, cachexia, and failure to thrive—typically in the first decade of life. Large polyps can cause altered bowel habits or obstruction. The most serious complication later in life is colorectal cancer, and the average age for the diagnosis of cancer is 34 years, so anemia and obstruction in these patients should trigger an alarm.

The Genetic Basis of JPS

There is a bewildering heterogeneity in the genetic causes of JPS, and different estimates of the genetic causes have been reported from different institutions. The two genes most likely to be responsible for JPS are the *bone morphogenic protein receptor 1A* (*BMPR1A*), which may account for 38% of cases, and the *SMAD4* gene (also called *MADH4* or *DPC4,* because of its independent discoveries by different groups), which was once reported to account for most cases, but revised estimates are in the vicinity of 15%. The *Phosphatase and TENsin homologue deleted on chromosome 10* (*PTEN*) gene was initially thought to account for some cases of JPS, but the deletions of this gene on chromosome 10q in some families may have been a reflection of the loss of the nearby *BMPR1A* gene in the same location. In other cases, there have been mutations of *PTEN*, but the cases may have been misdiag-

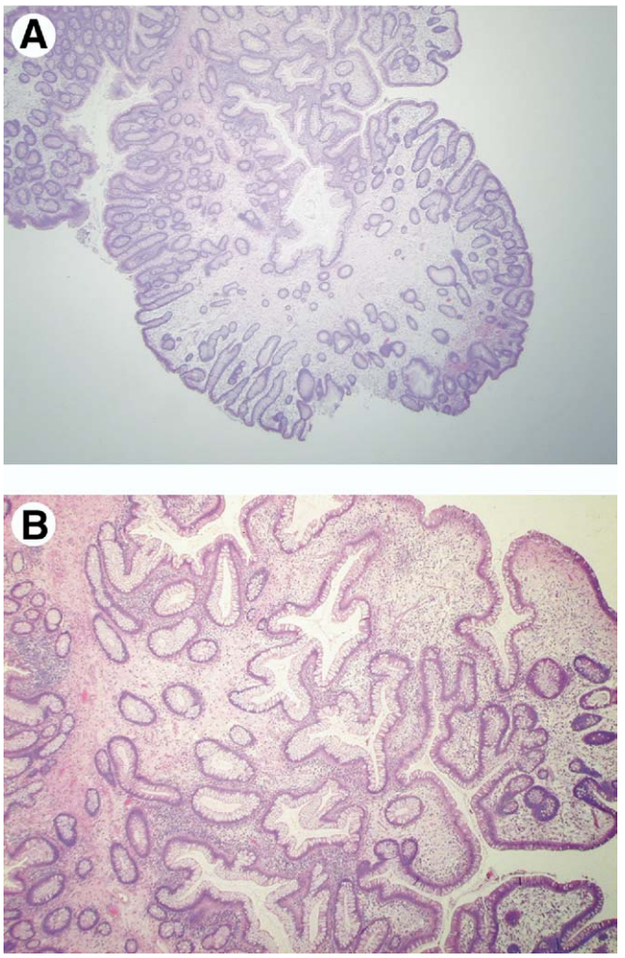

Figure 1 Juvenile polyp from the colon. This photomicrograph demonstrates the characteristic features of the juvenile polyp, including the smooth surface covered with a single layer of columnar epithelium, cystic dilation of the glands within the polyp, edema of the lamina propria, and a mild inflammatory infiltrate within the lamina propria. Sporadic juvenile polyps are indistinguishable from those in JPS. (A) Low power view of a juvenile polyp showing the normal-appearance to the superficial epithelium over an expanded lamina propria with a large, central cystic gland. (B) Higher power view of the juvenile polyp showing the benign appearance to the epithelium, the increased volume of lamina propria, containing an increased number of inflammatory cells. The authors gratefully acknowledge Richard Meyer, MD, Department of Pathology, Baylor University Medical Center for the photomicrographs. (Color version of figure is available online.)