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EDITORIAL

Peutz-Jeghers syndrome: Diagnostic and therapeutic approach

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Abstract

Peutz-Jeghers syndrome (PJS) is an inherited, autosomal dominant disorder distinguished by hamartomatous polyps in the gastrointestinal tract and pigmented mucocutaneous lesions. Prevalence of PJS is estimated from 1 in 8300 to 1 in 280 000 individuals. PJS predisposes sufferers to various malignancies (gastrointestinal, pancreatic, lung, breast, uterine, ovarian and testicular tumors). Bleeding, obstruction and intussusception are common complications in patients with PJS. Double balloon enteroscopy (DBE) allows examination and treatment of the small bowel. Polypectomy using DBE may obviate the need for repeated urgent operations and small bowel resection that leads to short bowel syndrome. Prophylaxis and polypectomy of the entire small bowel is the gold standard in PJS patients. Intraoperative enteroscopy (IOE) was the only possibility for endoscopic treatment of patients with PJS before the DBE era. Both DBE and IOE facilitate exploration and treatment of the small intestine. DBE is less invasive and more convenient for the patient. Both procedures are generally safe and useful. An overall recommendation for PJS patients includes not only gastrointestinal multiple polyp resolution, but also regular lifelong cancer screening (colonoscopy, upper endoscopy, computed tomography, magnetic resonance imaging or ultrasound of the pancreas, chest X-ray, mammography and pelvic examination with ultrasound in women, and testicular examination in men). Although the incidence of PJS is low, it is important for clinicians to recognize these disorders to prevent morbidity and mortality in these patients, and to perform presymptomatic testing in the first-degree relatives of PJS patients.

Key words: Gastrointestinal endoscopy; Intraoperative period; Peutz-Jeghers syndrome; Hamartoma

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INTRODUCTION

Peutz-Jeghers syndrome (PJS) belongs among the most important familial hamartomatous polyposis syndromes, and is associated with significant morbidity, variable clinical course and considerable predisposition to malignancy. This editorial will attempt to give an overview of up-to-date knowledge on diagnostic and therapeutic aspects of this disease.

DEFINITION AND HISTORY OF PJS

PJS is an inherited, autosomal dominant disorder with variable inheritance, characterized by hamartomatous polyps in the gastrointestinal tract, mostly in the small bowel, and pigmented mucocutaneous lesions. PJS was first reported in a pair of identical twins with melanotic macules described by Connor in 1895 and illustrated by Hutchinson in 1896[1,2]. Later in life, the twins developed what are now known to be additional features of PJS; one died of intussusception at age 20 years, and the other died of breast cancer at the age of 52 years[3,4].

The primary description of PJS was published by Peutz in 1921 in one Dutch family (the Harrisburg family)

as a gastrointestinal familial polyposis with pigmentations. Simultaneously occurring nasal polyposis was described in the original report by Peutz[5]. The pedigree of this original Dutch family continues to be followed[6,7]. Jeghers specified the description in 10 cases from different families in his work in 1949, and defined the relations between pigmented lesions, gastrointestinal polyposis and increased risk of carcinoma; approximately half of his patients suffered from gastrointestinal malignancy[3]. The eponym PJS was first used in 1954[8]. The first histological description of hamartomatous polyps was made in 1957 by Horrilleno and colleagues[9]. Since this time, descriptions have appeared of several different syndromes with the propensity to develop these polyps in the upper and lower gastrointestinal tracts. The hamartomatous polyposis syndromes are a heterogenous group of disorders, which are inherited in autosomal dominant fashion. These syndromes include familial juvenile polyposis syndrome, PJS, phosphatase and tensin homolog gene (PTEN) hamartoma tumour syndromes (Cowden's and Bannayan-Riley-Ruvalcaba syndromes), multiple endocrine neoplasia syndrome 2B, hereditary mixed polyposis syndrome, Cronkhite-Canada syndrome, basal cell nevus syndrome, and neurofibromatosis 1. The hamartomatous polyposis syndromes represent only a small number (< 1%) of the inherited gastrointestinal cancer predisposition syndromes[10,11].

A history of PJS with biographies of Peutz and Jeghers has been published[12], and many early PJS papers have been made available online by the Jeghers Medical Index (www.jeghers.com/pj_pubmed.aspx). The website www.peutz-jeghers.com is another resource for PJS patients and healthcare providers.

Association of Cancer Online Resources (ACOR) is a large collection of cancer-related internet mailing lists, which have delivered over 1.5 million e-mail messages per week to subscribers across the globe. In addition to supporting the mailing lists, ACOR develops and hosts state-of-the-art internet-based knowledge systems that allow the public to find and use credible information relevant to their illness (PJS Online Support Group, http://listserv.acor.org/archives/pjs.html).

PREVALENCE

The estimation of population prevalence of PJS differs between studies. The widest estimated range is from 1 in 8300 to 1 in 280 000 individuals[11,13-18]. Probable prevalence is around 1 in 100 000 people. The disease has variable penetrance, even within families; some members will only manifest hyperpigmentation, while others may manifest pigmentations and hamartomatous polyps.

Very important data are available thanks to different registries of polyposis. The St. Mark's Polyposis Registry (www.polyposisregistry.org.uk) is the oldest in the world. This was started in 1924 by Dr. Cuthbert Dukes and Mr JP Lockhart Mummery. The statement made by Dr. Dukes in 1958 remains true today: *"It would be difficult to find a more promising field for the exercise of cancer control than a polyposis family, because both diagnosis and treatment are possible in the precancerous stage and because the results of surgical treatment are excellent"*.

The Danish Polyposis Register was established in 1971 and the register became national in 1975.

American Family History Registries are also available on the net: www.fascrs.org/patients/family_history_registries/.

GENETICS AND PATHOPHYSIOLOGY

Genetic testing is suitable for confirmation of PJS. Nowadays, the only identifiable mutations causing PJS affect the STK11 (serine/threonine-protein kinase 11 alias LKB1) gene, located on chromosome 19p13.3. STK11 is the official designation for LKB1 by the Human Genome Organisation (HUGO); www.genenames.org/data/hgnc_data.php?hgnc_id=11389. This gene was identified in 1998. It encodes for a multifunctional serine-threonine kinase, important in second messenger signal transduction. The serine-threonine kinase modulates cellular proliferation, controls cell polarity, and seems to have an important role in responding to low cellular energy levels[15,19]. In the performance of this last role, the STK11 protein is involved in the inhibition of AMP-activated protein kinase (AMPK), and signals downstream to inhibit the mammalian target of rapamycin (mTOR; also known as FKBP12-rapamycin complex-associated protein or FRAP) pathway; the mTOR pathway is dysregulated in patients with PJS[15]. Although the exact mechanism of action of STK11 has not been outlined completely, the function of this protein product is likely to be important in growth inhibition. Genetic alterations in STK11 may represent loss of heterozygosity at a tumor suppressor gene locus.

Recent studies have suggested the involvement of STK11 also in more common human disorders including diabetes mellitus and in a significant fraction of lung adenocarcinomas. These observations have increased the interest towards the signaling pathways of this tumor suppressor kinase[20].

Genetic testing for STK11 mutations is available but they have variable sensitivity; in familial cases, 70%, in sporadic cases, from 30% to 67%. A significant proportion of familial and sporadic PJS may result from mutations in genes other than STK11 or so far unidentified means of LKB1 inactivation. In total, 91% of the studied families have shown LKB1 inactivation[11,13,14,16,17,19,21-23]. Variable penetrance and clinical heterogeneity make it difficult to determine the exact frequency of PJS[24].

Germline mutations in the tumor suppressor gene PTEN (10q22-23) are responsible for a group of phenotypically diverse conditions, which have collectively been called the PTEN hamartoma tumor syndrome. These are rare autosomal dominant conditions different from PJS[13,22].

PATHOLOGY

The hamartomatous polyposis syndromes are chara-

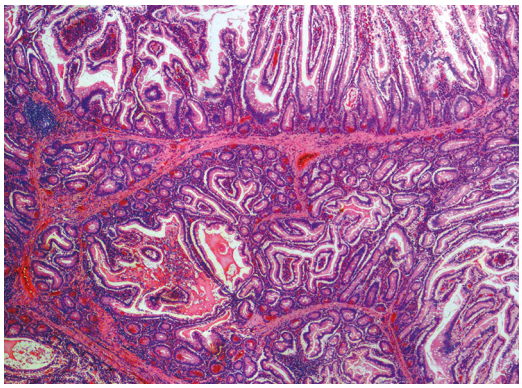

Figure 1 Hamartoma, a typical PJS polyp demonstrating the arborizing pattern of smooth-muscle proliferation. HE staining, magnification 100 ×. (Courtesy of Professor A. Ryska, MD, PhD).

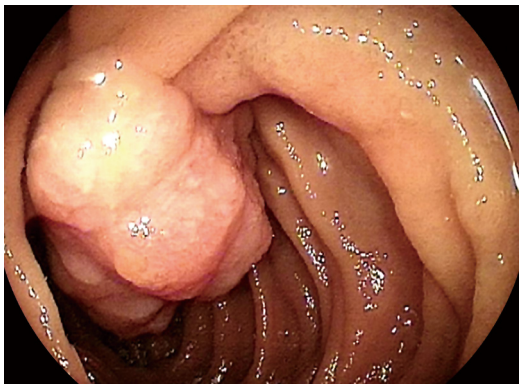

Figure 3 Hamartoma of the jejunum.

cterized by an overgrowth of cells native to the area in which they normally occur. It is important to note that there is an overgrowth of cells or tissues, at least initially, with no presumed neoplastic potential[14,22]. Hamartomatous polyps are composed of the normal cellular elements of the gastrointestinal tract, but have a markedly distorted architecture[11,15] (Figure 1). Microscopically, extensive smooth-muscle proliferation, with an elongated, arborized pattern of polyp formation, can be seen[15,16]. PJS-associated polyps can be differentiated from sporadic hamartomatous polyps and hamartomatous polyps associated with other syndromes by a unique smooth muscle core that arborizes throughout the polyp. PJS-type polyps do not have specific endoscopic features and can only reliably be distinguished from other types of polyps by histopathology. The unique PJS polyp pathology is best appreciated in PJS small intestine polyps[25]. The histopathology of PJS-associated gastric polyps can be similar to hyperplastic gastric polyps.

Larger hamartomas often contain foci of adenomatous tissue; a malignant development in a hamartomatous polyp has been described[7,26-28].

CLINICAL FEATURES AND NATURAL HISTORY OF THE DISEASE

Hyperpigmentation is present as mucocutaneous macules

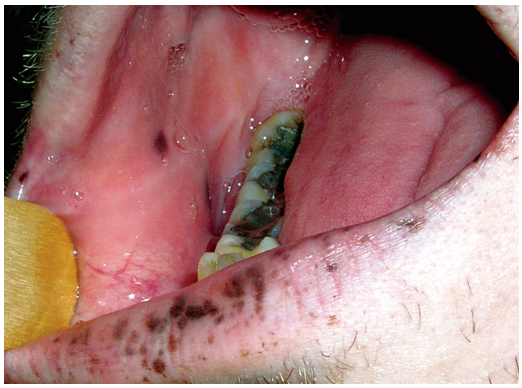

Figure 2 Pigmentations of the lips and oral mucosa.

on the lips (Figure 2) and around the mouth, eyes, nostrils, and on the buccal mucosa; and sparsely on the fingers, soles of the feet, palms, anal area and intestinal mucosa. Characteristic pigmentations are present in 95% of the patients and are caused by pigment-laden macrophages in the dermis. They are typically flat, blue-gray to brown spots 1-5 mm in size. Malignant degeneration of these lesions is extremely rare. These macules can be distinguished from common freckles as the latter never appear in the oral cavity, are sparse near the lips and nostrils, and absent at birth. Hyperpigmentations can even disappear during adolescence. Diagnosis is defined by the presence of histopathologically confirmed hamartomatous polyps (Figure 1) and at least two of the following clinical criteria: family history, hyperpigmentation and polyps in the small bowel[11,13-17,21,22,29] (Figure 3).

The median time to first presentation with polyps is about 11-13 years of age, and approximately 50% will have experienced symptoms by the age of 20 years[13,14]. During the first three decades of life, anemia, rectal bleeding, abdominal pain, obstruction and/or intussusception are common complications in patients with PJS[13,15]. Nearly half of the patients experience an intussusception during their lifetime, most often in the small intestine[30].

The setting of 222 patients with PJS was presented by Utsunomiya *et al*[31] in 1975. They presented patients with PJS in Japan ascertained between 1961 and 1974. The average age at diagnosis was 23 years in men and 26 years in women, with a male to female ratio of 1:1.13. Obstruction was observed in 42.8%, intussusception in 46.9%, most often in the small intestine, and rectal bleeding in 13.5% of the patients. The polyps occurred in the stomach in 48.6% (Figure 4A and B), small intestine 64%, colon 53.2%, and rectum 32%[31]. This study demonstrated the natural history of the disease despite this being based on surveys, and the study suffering some imperfections (e.g. cancer was found only in 28 of 222 patients).

Hearle *et al*[32] have published a study of STK11 status and intussusception risk in PJS. According to this study, 135 (60%) of the probands possessed a germline STK11 mutation, and 109 (48%) probands had a history of intussusception at a median age of 15.0 years but with wide variability (range: 3.7-45.4 years). Median

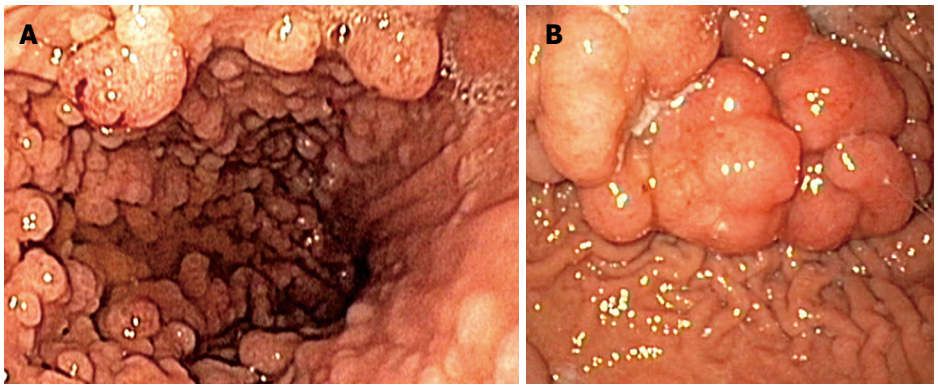

Figure 4 Hamartomas of the stomach. A: Multiple; B: Voluminous.

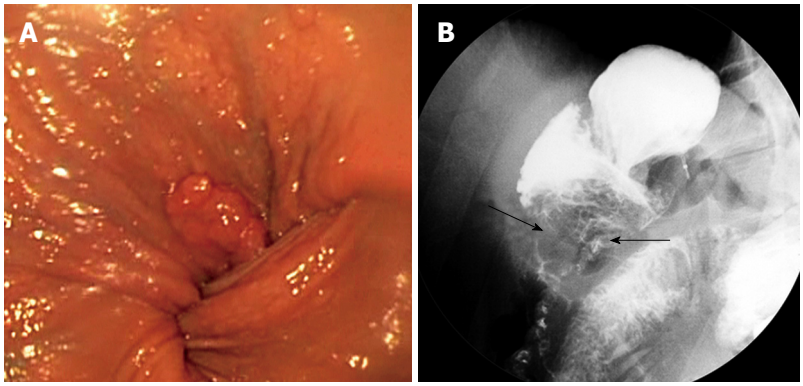

Figure 5 Gastric outlet obstruction (same patient as seen in Figure 4B). A: Endoscopic view; B: fluoroscopy, mass of polyps marked by arrows.

time to onset of intussusception was not significantly different between those with identified mutations and those with no mutation detected, at 14.7 and 16.4 years, respectively. Similarly, no differences were observed between patient groups on the basis of the type or site of STK11 mutation[32].

A quite rare but possible complication is gastric outlet obstruction caused by a giant gastric polyp[33-35] (Figure 4B and Figure 5). Children with PJS have a risk of numerous laparotomies due to the complications. Gastrointestinal screening of the small bowel should be started from childhood and when polyps develop they should be managed if possible by endoscopic resection[29,36]. 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[13,37,38]. Involvement of the colon (53% of patients), stomach (49%), and rectum (32%) is also seen[15,33-35]. Well-timed polypectomy may obviate the need for repeated urgent operations and extensive small bowel resections leading to short bowel syndrome[39,40].

Extraintestinal polyps are also reported. Nasal polyposis is thought to be a rare complication. de Leng *et al*[41] have observed nasal polyposis in eight (15%) of 52 Dutch patients with PJS. The loss of heterozygosity, and the absence of eosinophilia suggest a distinct pathogenesis compared with sporadic nasal polyposis. In the same study, 11 of 12 PJS-associated nasal polyps were found to express cyclooxygenase-2 (COX-2) compared with 19 of 28 sporadic nasal polyps[41]. Six of 22 members of the original Peutz pedigree have been diagnosed with nasal polyposis[6]. Three PJS patients have been reported with nasopharyngeal carcinoma[6,42].

In a series of 72 PJS patients, three (4.1%) had gallbladder polyps[43]. Also reported are one PJS patient who required cholecystectomy for gallbladder obstruction by polyps, and one with common bile duct obstruction caused by polyps[44]. Two PJS patients have been reported with gallbladder cancer; one of whom had gallbladder cancer arising near but not in hamartomatous gallbladder polyps[31,45]. Several PJS patients have been reported with bile duct cancer (cholangiocarcinoma)[46,47]. Hamartomatous polyps in PJS patients have also been reported in the ureter[48], respiratory tract[49,50] and on the tonsils[51].

PJS is associated with specific genetic mutations and an increased lifetime risk of both gastrointestinal and extraintestinal malignancies[22]; i.e. pancreatic, lung, breast, uterine, ovarian and testicular malignancies (Sertoli cell tumors secrete estrogen and can lead to gynecomastia). Inherited forms of gastrointestinal cancer have attracted the attention of scientists over the past two decades, putting the accent on prevention. The possibility of developing any cancer by age 65 years was 37% in accordance with data from the St. Mark's Polyposis Registry[52]. Hearle *et al*[53] have analyzed the incidence of cancer in 419 PJS patients, and 297 of them had documented STK11/LKB1 mutations. Ninety-six cancers were found among these patients. The risk for developing cancer at ages 20, 30, 40, 50, 60 and 70 years was 2%, 5%, 17%, 31%, 60% and 85%, respectively. The most common cancers represented in this analysis were

of gastrointestinal origin. In non-gastrointestinal tumors, breast cancer was the most common, with the risk being 8% and 31% at ages 40 and 60 years, respectively. The cancer risk was similar in the STK11/LKB1 mutation positive and negative group[53].

Mehenni *et al*[42] have followed the cumulative incidence of cancer in 149 PJS patients with germline mutation(s) in LKB1, this being estimated using Kaplan-Meier analysis of time to cancer onset, and compared between relevant subgroups with log rank tests. Thirty-two cancers were found in LKB1 mutation carriers. Overall cancer risks at ages 30, 40, 50, 60 and 70 years were 6%, 18%, 31%, 41% and 67%, respectively. There were similar overall cancer risks between male and female carriers. However, there were overall cancer risk differences for exon 6 mutation carriers *vs* non-exon 6 mutation carriers. Most (22/32) of the cancers occurred in the gastrointestinal tract, and the overall gastrointestinal cancer risks at ages 40, 50, 60 and 70 years were 12%, 24%, 34% and 63%, respectively. In female patients, the risk of developing gynecological cancer at age 40 and 50 years was 13% and 18%, respectively. Mutations in exon 6 of LKB1 were associated with a higher cancer risk than mutations within other regions of the gene[42].

In a meta-analysis of Giardiello *et al*[54], the cumulative risk of developing any cancer in PJS was 93%. Of all tumors associated with PJS, breast cancer poses the greatest risk, affecting 32%-54% of patients[54]. In their systematic study, Boardman *et al*[55] have determined that the relative risk for all cancers in PJS patients significantly increased (RR = 9.9). The relative risk for gynecological and breast cancers in women was 20.3, and for gastrointestinal cancers, 50.3[55]. Screening recommendations for PJS patients includes not only gastrointestinal multiple polyp resolution, but also regular cancer screening.

TREATMENT

There are two basic modalities in diagnosis and treatment of small bowel hamartomas: intra-operative enteroscopy (IOE) and double balloon enteroscopy (DBE).

DBE is a new enteroscopy method that allows examination and treatment of the jejunum and ileum in almost all patients. The system consists of a 200-cm enteroscope and a 145-cm over-tube which have soft latex balloons at their tips. By using these balloons to grip the intestinal wall, the endoscope can be inserted further without forming redundant loops of intestine[36].

IOE is a combination of laparotomy (or laparoscopy) with endoscopy. It allows manipulation to ensure the entire small bowel is visualized and nearly all polyps are removed in an endoscopic or surgical manner[17].

IOE was accepted as the ultimate diagnostic and/or therapeutic procedure for complete investigation of the small bowel, especially before the DBE era. A surveillance program published in the *British Journal of Surgery* in 1995 recommended IOE for small bowel polyps or abdominal pain in patients with PJS[22]. At that time, IOE improved polyp clearance without the need for additional enterotomy and helped to reduce the frequency of laparotomy[56] (Figure 6).

The first clinical application of DBE occurred in 1999 and was reported 2001 by its inventor Yamamoto *et al*[57]. DBE was established into clinical practice in 2003 and has taken the place of IOE for most indications. DBE is in most cases a suitable replacement for push enteroscopy, IOE, and to some extent, small bowel follow-through and computed tomography (CT)[58]. In spite of this, there is a small group of patients unsuitable for the DBE method. There could be some small intestinal adhesions after previous surgery making the DBE method impossible. It is necessary to inform all patients before DBE of possible surgical laparotomy with IOE or small bowel resection in case of failure of the DBE method[39].

It is necessary to clear away all small intestinal polyps as far as it is possible (at least all polyps greater than 5 mm). Oncel *et al*[59] have compared two groups of PJS patients. The first group of eight patients had only problem-focused surgery because of bleeding or obstruction. These patients required 23 further operations within 87 patient-follow-up-years (2.64 operations per year). The second group of three patients were operated upon using IOE, with removal of all small intestinal polyps. These patients did not require any further surgery within 21 patient-follow-up-years[59]. Timely clearance of all small intestinal polyps and careful screening is the gold standard for PJS patients.

IOE

IOE is still a useful method for a specific group of patients (e.g. failure of DBE, adhesions, multiple small transmural lesions unresolvable by endoscopic methods, carcinoids, and blue rubber bleb nevus syndrome) and therefore it is necessary to be able to use this method. We started with IOE in our department in 1995, where more than 7000 gastrointestinal endoscopies are accomplished per year. Over the course of the following years, the average need for this investigation stabilized to 6-8 per year. After launching DBE in March 2006 in our endoscopy unit, the need for IOE dropped to 1-2 cases per year.

IOE still remains a unique method of small bowel investigation and a solution for some pathological findings. The investigation is invasive, therefore, precise indication is imperative. The procedure takes place in the operating theater with close cooperation with surgical team. One of the advantages of IOE is that there is a surgeon on the other side of the small bowel wall. This allows the endoscopist to be more invasive and calmer. Perfect teamwork by the surgeon, endoscopist and anesthesiologist is indispensable.

The day before the investigation, a standard colonoscopy preparation of the bowel is performed (oral sodium phosphate or macrogolum solution). All patients are investigated under general anesthesia and intubated. Over-inflation of the stomach is prevented by introducing

a nasogastric tube for permanent suction at the beginning of the procedure. The physician performing the endoscopy becomes a member of the operating team. All our IOEs are performed using standard laparotomy with a mid-small bowel enterotomy. Polyps are removed preferentially in an endoscopic manner using a polypectomy snare. Some bigger polyps were removed by surgical excision because it was easier and less time-consuming. The characteristic technical details of IOE have already been presented[39].

DBE

DBE has an accessory channel and good manuverability in the distal small intestine, and it enables endoscopic treatment, including polypectomy. DBE is also useful for cases of difficult colonoscopy, providing success rates of total colonoscopy between 88%-100%. Although it has been a few years since its development, the usefulness of DBE is now well recognized. This challenging procedure has rapidly become popular and currently is used in many countries[60]. DBE is clinically useful for obtaining the diagnosis, starting treatment and providing therapeutic endoscopy. DBE is a useful and safe method of obtaining tissue for diagnosis and carrying out polypectomy[61].

The investigation is performed after overnight fasting using oral procedures, or after bowel preparation using standard colonoscopy preparation (oral sodium phosphate or macrogolum solution) and anal (retrograde) procedures. Total inspection by DBE usually is achieved by a combination of sequential oral and anal intubation; success rates are reported to be 40%-80%[60]. To confirm total enteroscopy, we use Indian ink tattooing of the small bowel. Total enteroscopy is also confirmed in the case of reaching the cecum by an oral approach, which is achieved in 10% of all oral DBEs in our setting.

We have used CO_2 insufflation in DBE procedures regularly sine 2007. We have had no complications with hyperinflation, the comfort of the patient rapidly increases, and this type of insufflation is helpful for easier and deeper insertion of the endoscope, because the absorption of CO_2 is 150 times faster than absorption of air in the bowel. Combination of water with simethicone is used routinely to do away with bubbles in the intestine.

Venous access is obtained before the procedure. All patients are monitored during the procedure, for oxygen saturation, heart rate, and blood pressure. Intravenous crystalloids are administered during DBE. Conscious sedation seems to be much better in DBE in comparison with general anesthesia. Abdominal pain is a very important warning signal, and it is necessary to terminate the procedure immediately in such cases. Intense pain may be a sign of inadequate pressure on the pancreas and high risk of post-DBE pancreatitis[62]. We use small intravenous repetitive doses of midazolam and pentazocine for conscious sedation (batch-wise).

The oral approach is preferred in all patients, because the number of polyps is significantly higher in the jejunum than the ileum. If panenteroscopy is not achieved by the oral approach, we perform Indian ink marking of the small bowel. Control capsule enteroscopy is performed subsequently to locate possible additional polyps in an uninvestigated part of the small bowel (in the distal small bowel below the Indian ink tattooing). After finding such additional polyps, we continue with oral DBE and complete the polypectomy.

Endoscopic therapy in the small intestine, whose wall is very thin, should be performed with special care to avoid complications such as bleeding and perforation[63]. To prevent bleeding, we use only pure coagulation for cutting of hamartomas with a long stalk. If the stalk is long enough to prevent hypercoagulation of the intestinal wall, this method is safe and very useful. However, this method must be abandoned for polyps with a short stalk or for sessile polyps. The use of too much coagulation could lead to hypercoagulation of the intestinal wall and perforation within a few days after the procedure.

Chemoprevention

Some recent studies have demonstrated the chemopreventive efficacy of rapamycin on PJS in a mouse model[64-66]. Rapamycin (sirolimus) is a macrolide compound with immunosuppressant properties that is obtained from *Streptomyces hydroscopicus*. Rapamycin treatment led to a dramatic reduction in polyp burden and size. A significant reduction in microvessel density was seen in polyps from the rapamycin-treated mice compared to those from the control group. The antiangiogenic effect of rapamycin may play a role in polyp reduction[66].

The potent antiproliferative activity of the macrolide antibiotic rapamycin is known to involve binding of the drug to its cytosolic receptor, FKBP12, and subsequent interaction with targets of rapamycin, resulting in inhibition of p70 S6 kinase. However, the downstream events that lead to inhibition of cell cycle progression remain to be elucidated. The antiproliferative effects of rapamycin are associated with prevention of mitogen-induced downregulation of the cyclin-dependent kinase inhibitor p27Kip1, which suggests that the latter plays an important role in the growth pathway targeted by rapamycin. Murine BC3H1 cells, selected for resistance to growth inhibition by rapamycin, exhibited an intact p70 S6 kinase pathway but had abnormally low p27 levels that were no longer responsive to mitogens or rapamycin. Fibroblasts and T lymphocytes from mice with a targeted disruption of the p27Kip1 gene had impaired growth-inhibitory responses to rapamycin. These results suggest that the ability to regulate p27Kip1 levels is important for rapamycin to exert its antiproliferative effects[67].

A pilot open-label study starts this year in the University of Utah and recruiting of participants *via* the internet (www.clinicaltrials.gov). Rapamycin analogs, which are already FDA-approved and are being used in more than 50 ongoing clinical trials, could one day be used for the treatment of PJS patients.

De Leng *et al*[68] have studied the presence of COX-2 in PJS. Moderate or high levels of epithelial COX-2 were present in 25% of hamartomas, including two hamartomas

with dysplastic changes, and 64% of carcinomas. The presence of COX-2 expression in PJS carcinomas and dysplastic hamartomas provides a rationale for chemoprevention with nonsteroidal anti-inflammatory drugs or COX-2 inhibitors. Focal immunohistochemical changes, which may indicate premalignant potential, were present in some nondysplastic PJS hamartomas. Molecular changes in carcinomas and dysplastic hamartomas in PJS are distinct from the usual adenoma-carcinoma sequence[68].

The study of Udd *et al*[69] was designed to determine whether COX-2 inhibition reduced tumor burden in Lkb1(+/-) mice or PJS patients. Genetic interactions between COX-2 and Lkb1 in polyp formation were analyzed in mice with combined deficiencies in these genes. Pharmacological inhibition of COX-2 was achieved by supplementing the diet of Lkb1(+/-) mice with celecoxib. In PJS patients, COX-2 was inhibited with a daily dose of 2 × 200 mg celecoxib for 6 mo. Total polyp burden in Lkb1(+/-) mice was significantly reduced in a COX-2(+/-) (53%) and in a COX-2(-/-) (54%) background. Celecoxib treatment initiated before polyposis (3.5-10 mo) led to a dramatic reduction in tumor burden (86%) and was associated with decreased vascularity of the polyps. Late treatment (6.5-10 mo) also led to a significant reduction in large polyps. In a pilot clinical study, a subset of PJS patients (2/6) responded favorably to celecoxib with reduced gastric polyposis[69]. Both studies suggest that COX-2 chemoprevention is beneficial in the treatment of PJS.

Metformin has been shown to inhibit mTOR activity in breast cancer cells but is unable to inhibit mTOR in cells that lack STK11[70,71]. Based on these data, it is unclear how effective metformin would be in PJS patients who are germline haplo-insufficient for STK11 and in PJS neoplastic tissue that does not express STK11.

Lifestyle factors including excess weight, lack of exercise, smoking, and alcohol use are risk factors for the cancers associated with PJS. Although no study of PJS patients has shown that modification of these risk factors reduces cancer risk, all PJS patients should be advised to adopt a healthy lifestyle.

OVERALL EXPERIENCE OF PJS PATIENTS

New endoscopic technology may improve management of intestinal polyposis[24,37]. Nowadays, DBE in combination with capsule enteroscopy are the gold standard for diagnosis and treatment of the small bowel[72]. These methods have replaced IOE in nearly all patients with PJS. Until only recently, primary surgical resection and IOE were the only available possibilities for treating polyps in the mid-small bowel in patients with PJS[73-76]. DBE and video capsule enteroscopy have changed this approach and it is now possible to not only to perform endoscopic surveillance and diagnose these lesions, but also to resect them[37,58,73,77,78]. Many reports on DBE have suggested that this new method may be able to replace at least IOE in many circumstances[63,79,80].

Indications of IOE have diminished over recent years because of the development of DBE[57]. Despite its current introduction into clinical practice[80-82], IOE is reserved for those cases in which DBE cannot be performed or fails to investigate the entire small intestine, especially to prevent excessive bowel resection. The advantages and disadvantages of IOE and DBE methods are summarized in Table 1.

Table 1 Benefits and drawbacks of endoscopic methods[39,77]

Method	Intra-operative enteroscopy	Double balloon enteroscopy
Benefits	All polyps removed in one procedure	Less invasive
	Partnership with a surgeon	Well tolerated
	Less time-consuming for endoscopist	Shorter sick leave
Drawbacks	Necessity of laparotomy	Often more than one procedure required
	Possibility of adhesions formation	Not feasible in some patients (because of adhesions)
	Longer convalescence	Longer procedure

Pennazio *et al*[83] have followed seven patients during a 10-year period. During the first period, five patients underwent emergency small bowel resection (two were operated on twice). Subsequently, three of four patients with diffuse polyposis underwent IOE during which, on average, 16 polyps per patient were removed (range: 10-25 polyps; mean diameter: 16 mm, range: 3-50 mm). The other three patients with polyps only in the proximal jejunum underwent periodic push enteroscopy alone (mean: three per patient), during which, a mean of 12 polyps per patient were removed (range: 7-15 polyps; mean diameter: 11 mm, range: 3-40 mm)[83].

From 1999 to 2006 we performed seven IOEs in seven patients (four women and three men) in our single tertiary center. A total number of 182 polyps were removed during IOE; 179 by an endoscopist and three by a surgeon. From six to 75 polyps were removed per session (mean: 26). The largest hamartoma measured 4 cm in diameter. The age of the patients ranged from 20 to 50 years (mean: 31 years). The mean time of the endoscopic part of the procedure was not measured exactly; it was estimated at 60 min. We had no serious complications in the IOE group.

From 2006, we accomplished 11 DBEs in another seven PJS patients (five women and two men). In our DBE group, a total of 205 polyps were removed. The age of the patients ranged from 12 to 48 years (mean: 25 years). From one to 37 polyps were removed per session (mean: 13). All polyps were resolved using the endoscopic method (snare polypectomy). The largest hamartoma was 6 cm in diameter and was removed by a piecemeal technique without complications. The mean time required to carry out the DBE procedure was 113 min (range: 20-270 min). All patients from the DBE group were resolved by means of endoscopic polypectomy; none of them had to be operated on. We had no serious complications in the DBE group.

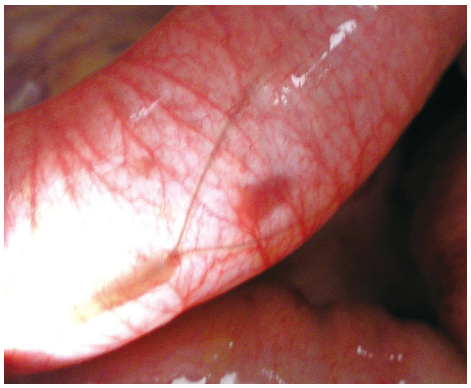

Figure 6 Intra-operative enteroscopy. Polypectomy snare over a small polyp shines through the intestinal wall.

The endoscopist performing DBE should be trained not only in endoscopy, but also in polypectomy. He/she must be experienced and be able to resolve complications[73,77]. Moreover, it is necessary to have close collaboration with a surgeon in case of complications. Complete polypectomy in IOE or DBE can provide a longer symptom-free interval[39,40,77].

In the series published to date, complications of DBE solely relating to the diagnostic procedure are rare. A recent retrospective multicenter survey in four countries has indicated a complication rate of 0.8% (13/1728) in diagnostic procedures and 4.3% (27/634) for therapeutic DBE, and there were no fatal cases[63,84,85].

During DBE, careful attention must be paid not to insufflate too much air, because this induces intestinal loop formation and impedes deep advancement[73]. With CO_2 insufflation, we solved this problem completely. Hyperinflation in combination with oxygen desaturation is a common complication according to the literature[73]. Continual monitoring during the procedure is indispensable.

Quite a common complication could be bleeding after polypectomy[73]. We do not consider it to be serious if the patient's blood count does not drop and if the bleeding is resolved by the endoscopist without surgical support in the case of DBE.

A feared complication is perforation after polypectomy. Perforation has been reported in 2%-6.5% of patients[74,75]. Polypectomy of large polyps appears to be the procedure associated with the highest risk[74].

FOLLOW-UP AND MALIGNANCY SCREENING

It is necessary to find the optimal method for screening of small intestinal polyps. Previously, the only method was enteroclysis (Figure 7A). Recently, wireless capsule endoscopy has been found to detect more polyps than small bowel radiographic studies (Figure 7B). Capsule enteroscopy is a feasible, safe and sensitive test for small bowel surveillance in patients with PJS, even in children. It is significantly more comfortable than barium

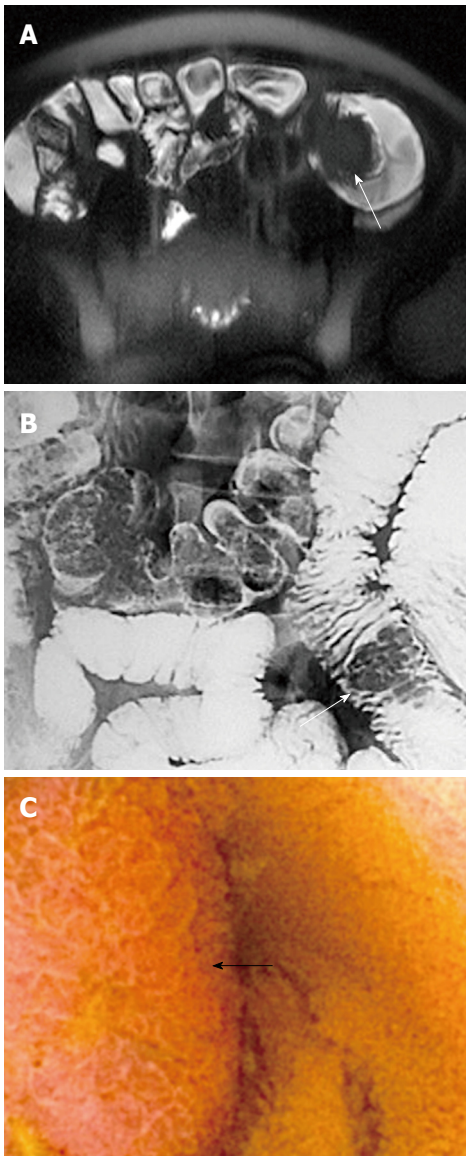

Figure 7 Hamartoma of the jejunum (arrow). A: Magnetic resonance imaging; B: Enteroclysis; C: Capsule enteroscopy.

enterography[86,87]. The use of capsule endoscopy permits earlier diagnosis, therefore, the clinical course of intestinal polyps has changed. These polyps are now seen before the occurrence of obstructive signs. Capsule endoscopy can detect polyps in the entire length of the small intestine, with a higher diagnostic yield compared to CT and magnetic resonance imaging (MRI) with enteroclysis, particularly for lesions less than 1 cm in diameter[88]. CT is another option for screening. CT with oral contrast has demonstrated greater sensitivity than small bowel radiography[13]. In our opinion, MRI with oral contrast is superior to CT, not only to prevent high doses of radiation in young people during CT, but also for higher accuracy of MRI enteroclysis. Unlike capsule endoscopy, MRI enteroclysis can determine the exact size of bigger polyps (Figure 7C). On the other hand, capsule enteroscopy is more successful in finding small polyps. That is why we prefer a combination of both these methods, as do many others[73,87,89].

All PJS sufferers have to be enrolled for lifelong

Table 2 Cancer screening in PJS patients[13-17,22]

Site of possible tumour	Age of screening initiation	Periodicity	Method of screening
Colon	15 yr[1]	2 yr[2]	Colonoscopy, CA 19-9
Oral parts of GIT	15 yr[1]	2 yr[2]	Gastroscopy
Small intestine	15 yr[1]	2 yr[2]	Capsule enteroscopy or MRI scan
Breast	21 yr	Monthly	Self-examination
		6-12 mo	Sonography or mammography, CA 125
Thyroid gland	18 yr	1 yr	Sonography, clinical examination
Pancreas	18 yr	1 yr	Sonography or CT or MRI scan
Uterus and ovaria	18 yr	1 yr	Sonography, clinical examination
Testes	18 yr	1 yr	Sonography, clinical examination
Lung	18 yr	5 yr?	X-ray, clinical examination

[1]Earlier in symptomatic persons; [2]Endoscopy each year as long as polyps are present, subsequently prolong intervals. PJS: Peutz-Jeghers syndrome.

screening because of the high risk of different carcinomas (Table 2). There have been some case reports in the literature of the occurrence of malignancy in very young patients, even in children[38,90].

There is no consensus or organization-approved guidelines for cancer surveillance in PJS patients. Different protocols are used at Johns Hopkins Hospital[91], St. Mark's Hospital[92], the Mayo Clinic[93], the University of Edinburgh[94], Danish Polyposis Registry[95], and the University of Newcastle (Australia)[96]. There are many differences between the protocols, but whichever protocol is used, it should be modified according to available resources, the individual patient's disease manifestations, psychosocial situation, and personal preferences.

It is necessary to perform consistent screening for possible malignancies in all patients with PJS: colonoscopy, upper endoscopy, CT, MRI or ultrasound of the pancreas, chest X-ray, mammography and pelvic examination with ultrasound in women, testicular examination in men, carbohydrate antigen 19-9 (CA-19-9), and cancer antigen (CA 125)[52-55].

DBE together with capsule endoscopy are essential modalities for the management of small intestinal diseases. IOE is the ultimate method in those patients in whom complete DBE investigation is impossible because of adhesions or other technical complications. IOE will be reserved for those cases in which DBE could not be performed or fails to investigate the entire small intestine, especially to prevent excessive bowel resection[39,77].

We currently perform all of these methods in our department: push-enteroscopy, DBE, IOE and wireless capsule endoscopy. We do not consider these methods competitive but complementary for proper indications.

Last but not least, the psychosocial impact of PJS is very important and deserves special attention. Results have shown that PJS patients suffer from mild depression even though physically they did not feel any impact from their condition compared to the general population. However, having PJS causes them to alter many important life decisions. This fact is important in developing a plan for care of these patients regarding genetic counseling and surveillance strategies for PJS patients[16,97].

It is even possible to treat benign hyperpigmentation of the face by means of laser therapy. Q-switched lasers are the preferred method. The treatment is effective[98], but this is only complementary cosmetic therapy.

CONCLUSION

In summary, timely polypectomy, preferably using the DBE method, are essential for patients with PJS. Follow-up of gastrointestinal polyps is necessary. The best combination of methods is capsule enteroscopy and MR enteroclysis. Lifelong screening of malignancies is indispensable on a regular basis. It is necessary to investigate all first-degree relatives of the patient. Although the incidence of PJS is low, it is important for clinicians to recognize these disorders to prevent morbidity and mortality in these patients, and to perform presymptomatic testing in patients at risk.

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