

## Peutz-Jeghers Syndrome: Data from the Singapore Polyposis Registry and a Shifting Paradigm in Management

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### Abstract

**Introduction:** Peutz-Jeghers Syndrome (PJS) is an uncommon autosomal dominant hamartomatous polyposis syndrome. Morbidity arises from polyp-related complications and increased risks of malignancy. We report on PJS patients registered in the Singapore Polyposis Registry, identified principal causes of morbidity and appraised current management strategies. A follow-up protocol based on recent literature has been proposed. **Materials and Methods:** A search of a prospectively collected database in the Singapore Polyposis Registry was made. Only patients who fulfilled the diagnostic criteria of PJS were included. The clinical records were retrieved for review. Information on affected family members was obtained from the Registry's pedigree records. **Results:** Seven unrelated patients fulfilled the criteria of having PJS. Principal causes of morbidity include recurrent bouts of abdominal colic, episodes of intestinal obstruction, gastrointestinal bleeding and the need for repeated laparotomies. Six out of 7 patients had initial presentation with acute intestinal obstruction requiring emergency laparotomy. Management was mostly problem-oriented and marked inter-surgeon variation with regard to cancer screening and genetic counselling was observed. **Conclusion:** Patients with PJS suffer gastrointestinal complications from polyposis and are at increased risks for developing cancers. A move towards surveillance and planned comprehensive care may reduce the morbidity of the condition. A protocol driven approach conducted in the setting of a Polyposis Registry is ideally suited to facilitate such care.

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### Introduction

Peutz-Jeghers Syndrome (PJS) is an uncommon autosomal dominant hamartomatous polyposis syndrome associated with mucocutaneous melanocytic macules. Melanin deposition occurs most commonly in the perioral region and buccal mucosa, but these macules may also be found on the hands, feet and perianal regions.<sup>1,2</sup> Patients with PJS are also at increased risk for developing malignancies of the luminal gastrointestinal organs, pancreas, lungs, breasts and reproductive organs.<sup>3-6</sup> We report on the PJS patients registered in the Singapore Polyposis Registry, highlighting patterns of presentation and the principal causes of morbidity and management to date in our local population. We reviewed the current literature and proposed a shift from the traditional reactive problem-oriented surgery to employing a preventive combined surgical-endoscopic approach in the management of diffuse small bowel polyposis.

### Materials and Methods

A search of a prospectively collected database in the Singapore Polyposis Registry (started in 1989) containing 610 patients with intestinal polyposis was made. Data collection was based on voluntary reporting by participating clinicians islandwide. Only patients who fulfilled the diagnostic criteria of PJS were included in this study, that is, having histopathologically confirmed hamartomatous polyps and at least 2 of the following clinical criteria: i) family history, ii) mucocutaneous hyperpigmentation, and iii) small bowel polyposis.<sup>5</sup> Seven patients with PJS were identified. Their clinical records were retrieved for review. Information on affected family members was obtained from the Registry's pedigree records.

### Results

All 7 index patients had small bowel hamartomatous polyps confirmed on histology and peri-oral pigmented

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macules at presentation. Three patients (43%) had family members with diagnosed PJS or medical histories suggestive of PJS. The remaining 4 (57%) had no known family history of PJS. Four were ethnic Chinese and the remaining Malay. The male-to-female ratio was 1: 2.5. The median age at diagnosis was 19 years (range, 7 to 34). The median time of follow up from diagnosis was 110 months (range, 14 to 183). Patient characteristics and clinical symptoms are summarised in Table 1.

Acute intestinal obstruction secondary to complication of small bowel polyposis was the commonest initial clinical presentation, occurring in 6 patients (86%). Eventually, all had at least 1 episode of acute intestinal obstruction requiring emergency laparotomy. One patient required 2 laparotomies, 1 had 3, and another had 4 laparotomies for intestinal obstruction secondary to intussusception due to a polyp. Depending on bowel viability, simple reduction of the intussusception with polypectomy or resection of the non-viable bowel was performed. Six (86%) patients had small intestines resected. None developed short-gut syndrome. One patient required a laparotomy for adhesive obstruction.

All 7 patients reported at follow-up to have frequent episodes of abdominal colic – possibly related to residual polyp burden or postoperative adhesions. Two patients had multiple hospital admissions postoperatively for severe abdominal pain.

Gastrointestinal bleeding with anaemia was a significant morbidity in 42% (n = 3) of our cohort. One had haematochezia as the presenting complaint. Colonoscopy revealed haemorrhoids and multiple sigmoid polyps which proved to be of the Peutz-Jeghers hamartomatous type on histology. Gastroscopy in the same patient showed no ulcers, just hamartomatous polyps at various sites in the stomach and duodenum. In our Registry, 2 patients had recurrent overt bleeding manifesting as haematochezia and melena. These patients had numerous polyps throughout the gastrointestinal tract. One had recurrent occult gastrointestinal bleeding with persistent symptomatic anaemia.

In the absence of a standardised management protocol, individual surgeons determined patient management based on a problem-oriented approach. Intervention was performed only upon acute complication related to the polyp and this usually necessitated a laparotomy. Surveillance of small bowel polyposis between acute presentations was not routinely undertaken, with only 3 patients having either a contrast study in the past or capsule endoscopy when this modality became available recently. Cancer screening, if done, varied in type and frequency and seldom included all the cancers to which PJS patients are at increased risk of developing. Screening for gastrointestinal malignancies was the only one performed consistently, with 6 patients having regular (1 to 2 yearly) upper and lower gastrointestinal endoscopies. Small bowel surveillance was done for 3 patients; pancreatic imaging for 1, and 1 had regular mammograms. Only 2 patients (28%) received genetic counselling. None of the family members in this cohort was investigated for PJS.

## Discussion

Peutz-Jeghers Syndrome is a rare autosomal dominant inherited hamartomatous polyposis syndrome associated with mucocutaneous melanocytic macules.<sup>1,2</sup> Individuals are at increased risks of intestinal and extraintestinal malignancies such as pancreatic, breast, uterine, ovarian and testicular carcinomas.<sup>3-7</sup> The prevalence of this condition is estimated to be 1 in 200,000, and penetrance is variable, even within families.<sup>6,7</sup> The prevalence and clinical presentation of this group of patients in Singapore has never been thoroughly described. In this review, we report on PJS patients registered in the Singapore Polyposis Registry, focussing on the principal causes of morbidity in our patient cohort and appraised our current management strategies. A new follow-up protocol based on a review of recent literature has been proposed.

Giardiello et al<sup>5</sup> defined a definitive diagnosis of PJS by the presence of histopathologically confirmed hamartomatous polyps and at least 2 of the following clinical criteria: (i)

Table 1. Characteristics and Clinical Morbidity of PJS patients in the Singapore Polyposis Registry

	Gender	Race	Year registered	Age of presentation (y)	Abdominal pain	Intestinal obstruction	Haematochezia/Melena	Significant occult bleeding	No. of laparotomies	Bowel resection
Case 1	Male	Chinese	1984	34	+	+	+	-	1	+
Case 2	Female	Malay	1988	17	+	+	-	+	2	+
Case 3	Female	Chinese	1998	7	+	+	-	-	3	+
Case 4	Male	Malay	1998	27	+	+	-	-	1	-
Case 4	Female	Chinese	2003	10	+	+	-	-	1	+
Case 6	Female	Malay	2004	22	+	+	-	-	1	+
Case 7	Female	Chinese	2005	16	+	+	+	+	4	+

family history, (ii) hyperpigmentation or (iii) small bowel polyposis.

### *Gastrointestinal Polyposis*

Gastrointestinal hamartomatous polyps occur in 88% to 100% of patients with PJS.<sup>8</sup> These polyps are most frequently present in the small intestine (64% to 96%), with the heaviest polyp burden in the jejunum followed by the ileum and the duodenum in descending order.<sup>1,9,10</sup> Bartholomew et al<sup>10</sup> reported in their series of 182 cases, 96% small bowel polyposis, 27% colonic polyps, 24% rectal polyps and 24% gastric polyps. In our series, all had small bowel polyps. Colorectal polyps were present in 5 patients and 5 had gastric polyps.

Gastrointestinal polyps typically develop around the time of early adolescence and are the cause of much of the clinical morbidity.<sup>1,7,9,11</sup> Hence, it is recommended that surveillance for gastric and small bowel polyposis begins at age 10 and continues at 2-yearly intervals. These gastrointestinal polyps are sources of blood loss when they ulcerate or infarct. Large volume blood loss may cause a patient to present with hematochezia or melena while chronic occult bleeding often manifest as symptomatic anaemia. Periodic surveillance and removal of larger polyps aim to reduce the likelihood of such complications. Two of our patients experienced limitations of physical activity due to chronic anaemia and required several hospital admissions for blood transfusions.

Sufficiently large polyps may act as lead points resulting in chronic and acute intussusceptions. Patients often suffer from bouts of abdominal colic, and acute intestinal obstructions requiring emergency surgery with resection of non-viable bowel is common.<sup>3,12,13</sup> Six out of 7 patients in this study had acute intestinal obstruction as their initial presentation. All 7 have had at least 1 laparotomy and 6 required varying amounts of bowel resection. These patients would likely experience additional laparotomies in their lifetime. Repeated laparotomies and extensive bowel resections often result in adhesions with intestinal obstruction and short bowel syndrome, adding further morbidity.

Upper and lower gastrointestinal endoscopies provide easy access to gastroduodenal and colorectal polyps, allowing for surveillance, polypectomies and other therapeutic manoeuvres. The management of small intestinal polyposis poses a greater challenge due to the technical difficulties of endoscopic access. Unfortunately, the burden of polyposis in PJS is greatest in the small intestines, and these polyps are responsible for much morbidity, especially at presentation. An effective strategy of managing small intestinal polyps is therefore necessary. The aims of systematic management of small intestinal polyps are to minimise the number of

laparotomies and episodes of bowel resections, as well as provide surveillance for the development of small bowel neoplasms to which PJS sufferers are predisposed. A small bowel series has traditionally been the commonly adopted method of choice to diagnose and monitor small bowel polyposis. However, this exposes the patient to repeated radiation which could be significant if used 2 yearly from the age of 10 years to survey the small bowel. Video capsule endoscopy for small bowel surveillance provides an attractive alternative in centres with the relevant expertise and facilities, although endoscopic or surgical means are still required for polyp removal.<sup>14,15</sup> Regular small bowel surveillance with early use of double-balloon enteroscopy (DBE) for prophylactic polyp removal is now an option.<sup>16</sup> In the elective setting, DBE with snare polypectomy has been shown to successfully remove small polyps detected on surveillance, thus avoiding the need for surgery. In a patient who has already undergone multiple laparotomies, severe adhesions may limit the safe use of DBE. The only option available for removal of large polyps in these patients who have had multiple prior laparotomies may be further laparotomies with the attendant risks of bowel injury necessitating further bowel resections. Therefore, there is every incentive to adopt a regular surveillance programme to avoid laparotomies, as this increases the chances of successful endoscopic control of polyposis and averts the risks of short bowel syndrome associated with repeated bowel resections. Offspring of the proband with small intestinal polyps, detected on small bowel series or capsule endoscopy, are likely to benefit most from DBE where early regular prophylactic removal of visualised small intestinal polyps may reduce the likelihood of subsequent acute presentation with intestinal obstruction or infarction. Magnetic resonance imaging (MRI) of the small bowel is another radiation-free method currently being evaluated for surveillance of small bowel polyposis. Its advantages include accurate determination of location and size of small bowel polyps larger than 5 mm.<sup>17</sup>

In cases that needed a laparotomy, a combined surgical-endoscopic approach for a “clean sweep” of the bowel has been advocated.<sup>8,18-20</sup> On-table endoscopy performed through an enterotomy made for surgical polypectomy allows the surgeon to guide the scope for complete examination of the large and small bowel. This direct visualisation of the mucosa is superior to intraoperative manual palpation for identification of hamartomatous polyps within the lumen of intestines, as these polyps are soft and of the same consistency as the bowel wall. Spigelman et al<sup>18</sup> demonstrated the inadequacy of conventional methods of identifying small bowel polyps by external palpation and transillumination in their study where 38% of polyps of significant sizes in 5 patients were overlooked. Apart

from better identification of polyps, endoscopic assessment also allows for all small polyps to be removed by snare polypectomy. For larger, thick-stalked or sessile polyps, open polypectomies via enterotomies may be performed. Strategically placed enterotomies along the small intestine allow segments of the small intestinal mucosa to be everted, facilitating open polypectomies throughout the entire length of the small intestine via a limited number of enterotomies. Long-term results from the St Mark's Hospital Polyposis Registry suggest that this "clean sweep" of all polyps allows for a longer symptom-free interval.<sup>19</sup> It also provides for histological surveillance for small bowel neoplasms.

### Cancer Surveillance

Patients with PJS are at increased risk for gastrointestinal and extraintestinal malignancies.<sup>1-5</sup> Giardiello et al<sup>4</sup> reported statistically significant increase in relative risk of cancers of the oesophagus, stomach, small intestine, colon, pancreas, lung, breast, ovary and uterus. The risk of developing pancreatic cancer in PJS has been estimated to be increased 100-fold. Screening and surveillance protocols for such individuals should then be considered separately from those recommended for people fulfilling low to moderate risk guidelines.

While reviewing the records of the 7 patients, we noted that methodical cancer screening for the relevant malignancies was often overlooked. This is due to the fact that patients were primarily referred from other institutions and compliance with recommendations for follow-up was inconsistent. The management of each patient was determined entirely by their individual surgeons, and only 2 patients had investigations or referrals for cancer screening. Clearly, the current management strategy in Singapore is suboptimal. While the cohort of patients in this review did not have reported cancers as a result of this absence in systematic screening, the body of evidence in the literature suggests that the cancer risk is significant in these patients. The lifetime risk of developing any cancer by age 64 is 93%, with lifetime breast cancer risk estimated to be 50%, pancreatic cancer 35%, colorectal cancer 20% to 40% and gastric cancer 30%.<sup>2,4</sup> It is thus reasonable to suggest that surveillance should be offered to these patients, and many international guidelines have adopted variations of such surveillance protocols.

Due to the very low prevalence of this condition, familiarity with PJS and its comprehensive management (including adequate cancer surveillance) may elude most clinicians. This highlights the need for a protocol driven approach in the management of these patients that is best coordinated through the Singapore Polyposis Registry. Such an approach will allow multi-disciplinary care to be delivered expeditiously and enable affected family members of the proband to be identified for optimal management.

Although an optimal screening strategy (including costs and benefits) has yet to be determined, various reviews have modified the protocol suggested by McGarrity et al.<sup>1</sup> A combination of regular clinical examination and specific investigations for the cancers frequently encountered in PJS is recommended (Table 2).

Table 2. Surveillance Guidelines for Peutz-Jeghers Syndrome

Site	Procedure	Onset age (y)	Interval (y)
Stomach	Upper endoscopy	10	2
Small bowel	Small bowel series, Enteroclysis or video capsule endoscopy	10	2
Colorectal	Colonoscopy	20	2-3
Pancreas	Endoscopic ultrasound/CT pancreatic protocol	30	1-2
Breast	Breast examination	25	1
	Mammography	25	2-3
Ovary, uterus	Pelvic examination	20	1
	Pelvic ultrasound	20	1
Testicle	Testicular examination	10	1

Laparotomy and peroperative enteroscopy is recommended for small bowel polyps larger than 1.5 cm, or abdominal pain with known small bowel polyps.

*Adjusted with modifications from references 1 and 2*

### Genetics

PJS has an autosomal dominant mode of transmission with up to 25% of documented non-familial cases.<sup>7</sup> To date, only mutations in the LKB1/STK11 gene located on chromosome 19p13.3 have been shown to cause PJS.<sup>21,22</sup> STK-11 acts as a tumour suppressor gene and encodes for a multifunctional serine-threonine kinase which is involved in the transduction of intracellular growth signals. Sporadic cases are thought to be due to de novo mutations in STK11. However, not all PJS patients have demonstrated mutations in the STK11 gene – a result that may reflect inadequacies of mutational analysis, the possibility of locus heterogeneity or a second gene causing PJS.<sup>21,22</sup>

While we await new genetic discoveries and the availability of genetic testing, the known genetic inheritance of this disease dictates that genetic counselling for individuals with PJS need to be addressed. Affected individuals should be educated on the genetic basis of their disease and the genetic burden to their offspring. Screening of family members and a detailed pedigree analysis for each patient will aid in identifying and managing yet-to-be diagnosed PJS individuals.

The Singapore Polyposis Registry was set up in 1989 under the mandate of the Ministry of Health, Singapore, to serve as

a central registry to all physicians in Singapore to facilitate the identification, surveillance and management of families and individuals with high risks of hereditary colorectal cancer. In our cohort, pedigree analysis was attempted for all by the Polyposis Registry. Family members were identified as possibly having PJS based on information of symptoms or known diagnoses as reported by the patient. However, none of the family members were voluntarily investigated for PJS. This could reflect reluctance on the part of patients making known their disease to their kindred, reticence of family members to be screened or lack of understanding about the genetic basis of this disease. In any case, adequate education that this disease has genetic consequences and identifying other affected family members is important, as PJS is not a completely benign disease given its potential for abdominal complications and risks of malignancies. The Singapore Polyposis Registry, with its Registry Coordinator and Genetic Counsellor, supported by the Colorectal Cancer Genetics Laboratory capable of genetic testing, is well poised to enhance the delivery of care to these families with uncommon hereditary polyposis syndromes. Multidisciplinary care involving Colorectal Surgeons, Gastroenterologists and Gynaecologists coordinated through the Polyposis Registry will further optimise the treatment and screening of organs at risk of cancer. Gene carriers have a 94% cumulative risk of gastrointestinal and extraintestinal cancers and lifelong cancer surveillance is advocated.<sup>4</sup> Patient support groups organised under the auspices of the Singapore Polyposis Registry may help in removing the fear and stigma associated with PJS and allow more family members to come forward for screening and predictive genetic testing. This will encourage compliance to intensive screening protocols in obligate gene carriers while removing the stigma and psychological impact on those who are gene negative.

## Conclusion

In the management of PJS, the small intestine is a non-renewable resource and this should prompt a paradigm shift – from a previously problem-focused management of polyposis-induced complications to planned, pre-emptive care. Regular early surveillance of the small bowel combined with polypectomy by DBE and the adjunctive use of intra-operative endoscopy to make a “clean sweep” of the bowel during surgery aim to maintain a low polyp burden in patients, minimising the occurrence of acute polyp-induced complications and prolonging the symptom-free interval. Screening for cancers associated with the PJS should also be done regularly for early detection. Optimal management requires a protocol driven approach best conducted through the Singapore Polyposis Registry, augmented by genetic testing and counselling of afflicted families.

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