Published in final edited form as:

J Pediatr Hematol Oncol. 2013 May ; 35(4): 323–328. doi:10.1097/MPH.0b013e318282db11.

Unusually early presentation of small-bowel adenocarcinoma in a patient with Peutz-Jeghers syndrome

Michael F. Wangler, M.D.^{1,*}, Rishikesh Chavan, M.D.^{*,2}, M. John Hicks, M.D., Ph.D. D.D.S.⁴, Jed.G. Nuchtern, M.D.^{3,5}, Madhuri Hegde, Ph.D.⁶, Sharon E. Plon, M.D., Ph.D.^{1,3}, and Patrick A. Thompson, M.D.^{2,#}

¹Department of Molecular and Human Genetics, Baylor College of Medicine

²Department of Pediatrics, Section of Hematology Oncology, Baylor College of Medicine

³Department of Pediatrics, Baylor College of Medicine

⁴Department of Pathology and Immunology, Baylor College of Medicine and Texas Children's Hospital

⁵Department of Surgery, Baylor College of Medicine

⁶The Department of Human Genetics, Emory University School of Medicine

Abstract

Peutz-Jeghers (PJS) syndrome is an autosomal dominant cancer predisposition syndrome characterized by melanotic macules, and hamartomatous polyps. Small-bowel surveillance in the pediatric PJS population is not designed to identify small-bowel malignancy which is thought to arise in adulthood. A 13 year old male presented with lead-point intussusception, requiring emergent surgical resection. A mucinous adenocarcinoma was found arising from high-grade dysplasia within a polyp. Based on these findings and mucosal pigmentation he was diagnosed with PJS. DNA sequencing revealed a heterozygous c.921-1G>T *STK11* mutation. This case is the earliest onset of small-bowel carcinoma in PJS, an observation relevant to surveillance guidelines.

Keywords

Peutz-Jeghers syndrome; *STK11*; small-bowel adenocarcinoma; lead-point intussusception; cancer surveillance

BACKGROUND

Peutz-Jeghers (PJS) syndrome is an autosomal dominant cancer predisposition syndrome characterized by melanotic pigmented macules, hamartomatous polyps and an increased risk of cancer ¹. The unusual pigmentation on the lips and its inherited nature has been clinically known since the report of "Hutchinson's twins" by British physicians Connor and

#Address for Correspondence: Patrick A. Thompson, MD, 6701 Fannin St, Texas Children's Cancer Center, Houston TX 77030, Phone: 832-824-4029, Fax: 832-825-1453, pathomps@txch.org.

*These authors contributed equally to this work

Conflicts of Interest: None declared

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Hutchinson, a finding which was assumed to be a curiosity¹. However, its relationship to cancer risk was suggested when one of these twins subsequently died of intestinal obstruction and the other of breast cancer. In 1949, Jeghers proposed that a single pleiotropic gene was likely responsible for this cancer predisposition syndrome². The diagnostic criteria of PJS are based on the clinical findings and require the presence of hamartomas and two of the following: 1) family history of PJS, 2) mucocutaneous hyperpigmentation, or 3) small bowel polyposis¹. PJS leads to life-threatening complications including lead-point intussusception due to the presence of the polyps and an array of solid tumors.

The genetics of PJS has been the subject of intensive study, and over time it has largely confirmed Jeghers proposed “single pleiotropic gene”². Germline mutations in the tumor suppressor gene *STK11* are identified in the majority of cases of PJS^{3,4}. While some authors have proposed the existence of other loci, *STK11* has been the only gene known to be associated with PJS. Both heterozygous point mutations and gene deletions of *STK11* are responsible for the PJS phenotype⁵. As molecular technology has advanced, cases which were previously classified as “*STK11* negative” were noted to be due to *STK11* deletions which were not detected by sequencing methods⁵. Recent studies combining diagnostic methods sensitive to deletions and point mutations have suggested that all cases may be due to some type of *STK11* mutation^{6,7}. The genotype-phenotype correlation in PJS is complex but higher cancer risk may be associated with mutations in exon 3 or premature truncation alleles⁸. While *STK11* is the only known gene, there are also no reported cases in which an individual with an *STK11* mutation does not show clinical manifestations leading some authors to suggest that these mutations are fully penetrant⁶. *STK11* is involved in epithelial polarity and in the regulation of proliferative signals of the mTOR pathway through phosphorylation of AMP kinase. The latter observation has led to promising therapeutic insight showing reduced polyp burden in PJS mouse models when treated with the mTOR inhibitor rapamycin⁹.

The gastrointestinal complications of PJS are significant and because of the possibility of malignant transformation of hamartomatous polyps present in the colon and small bowel, surveillance is recommended¹⁰. Current guidelines for GI tract surveillance are based on the expected age of onset of small bowel and colon cancers in PJS, generally after the second decade of life¹¹. In the pediatric population gastrointestinal surveillance is generally not undertaken although screening is recommended with follow-up if positive for polyps¹⁰. The risk of intussusception is significant for children and young adults with PJS⁸. Because of this the current recommendations for pediatric PJS patients suggest an initial endoscopy at age 8 years to evaluate for risk of obstruction, but subsequent screening which has been proposed involves contrast enema¹². This is proposed because of the risk of obstruction rather than cancer, and because of the high radiation burden it has not been uniformly adopted. In addition, tumor screening is not regularly initiated until after age 18 years¹⁰.

Here we report a case of a 13-year-old male who was first diagnosed with PJS after presenting with lead-point intussusception and was found to have a mucinous adenocarcinoma representing the earliest reported case of small bowel malignancy in PJS. We review the clinical course and the implications for surveillance guidelines for patients with PJS.

CASE REPORT

A 13 year old otherwise healthy Hispanic male developed sudden onset periumbilical abdominal pain which worsened over a 24 hour period. He had associated anorexia, and multiple episodes of watery brown emesis. He presented to an outside emergency

department where a CT scan demonstrated a “U-shaped” pelvic mass (11×5cm) with calcifications, concerning for teratoma or duplication cyst (Figure 1A, B), and a WBC count of 18,000. He was transferred to our institution for evaluation by pediatric surgery. Upon arrival he was ill appearing. On physical examination the patient was noted to have hyperpigmented macules over the lips, buccal mucosa, and similar macules on the fingertips (Figure 1C, D). Abdominal ultrasound revealed a large intussusception (Figure 1E). A comprehensive four-generation family history included four unaffected siblings and unaffected parents. The father’s maternal uncles were reported to have freckles on the face, although neither the father nor his mother had these findings and no photographs were available to confirm this report. There was no family history of GI abnormalities.

The patient was brought to the operating room for a diagnostic laparoscopy which revealed tightly distended loop of small bowel, felt to be small bowel intussusception. As this segment had to be resected the decision was made to proceed to an open procedure. The mesentery was divided and the segment was resected and was found to contain small bowel polyps, one of which was large and a likely pathologic lead-point. After resecting the involved segment an end-to-end anastomosis was performed.

Gross pathologic examination of the resected segment revealed a lead-point intussusception (Figure 2A). Mucosal polyposis was also evident (Figure 2B-D). The histology of this hamartomatous polyp was characteristic with extension of the muscularis propria into the substance of the polyp. (Figure 2D). In addition, an invasive mucinous adenocarcinoma was identified (Figure 3A-D), arising from an area of high-grade dysplasia within one of the polyps. This tumor was stage IIa (T3, N0, M0) with subserosal invasion (Figure 3E), and absence of lymph node involvement.

Due to the presence of malignancy a second operation with small bowel resection with 10 cm tumor free surgical margins and expanded lymph node sampling was performed. Follow up upper and lower endoscopy and imaging revealed additional hamartomatous polyps without evidence of additional primary masses or liver metastases. We concluded based on available evidence there was no indication for adjuvant chemotherapy or radiation therapy in our patient¹³. At last office visit two years after his initial diagnosis he was well without abdominal pain or other symptoms. He underwent capsule endoscopy approximately 1 year after diagnosis and is currently on a screening regimen involving capsule endoscopy every 2 years with additional studies to follow up the capsule endoscopy findings.

The patient’s diagnosis of PJS was confirmed by molecular testing. Sequence analysis of the *STK11* gene revealed a heterozygous c.921-1G>T (IVS8-1G>T) mutation. This mutation is pathogenic based on its predicted alteration of the splice acceptor site at the intron7/exon 8 boundary of the *STK11* gene and by its previous association with PJS¹³. Testing of the parents and siblings of the patient was declined by the family. The clinical impression was that this was a *de novo* case in this family given the highly penetrant nature of *STK11* mutations and the fact that the parents had never been affected with gastrointestinal complaints or mucosal pigmentation.

CONCLUSIONS

Peutz-Jeghers syndrome is an autosomal dominant condition which is thought to have an age-depending predisposition to gastrointestinal malignancy as well as other types of cancer. Adenocarcinoma in the GI tract is extremely rare in children. The incidence of adenocarcinoma of the colon in children is estimated to be 1 in 10 million¹⁴. Adenocarcinoma of the colon is associated with a number of genetic conditions in addition to PJS, including Familial Adenomatous polyposis, Hereditary non-polypoid colorectal

cancer (HNPCC) in addition to ulcerative colitis. Children that do develop adenocarcinoma of the colon are diagnosed at a later stage and have more aggressive histology because of delayed diagnosis¹⁴. Small bowel adenocarcinoma in children is even more rare with only a handful of cases reported¹⁵. Patients with PJS have an estimated cumulative risk of small bowel adenocarcinoma of 13% before age 64¹¹. The age of onset has varied between studies, but has uniformly been reported after the second decade^{11, 16}. In a study of 30 patients with PJS from Korea, four probands and four first-degree relatives of an affected proband had small bowel cancer, with an overall mean age of onset of cancer of 36 years¹⁷. In a large study of 240 patients with *STK11* mutations who were ascertained by positive family history of PJS, there was a 66% cumulative risk of all gastrointestinal tumors, however all occurred after age 20 years¹⁶. An extension of this study which included additional cases brought the total number of patients up to 419, but without any gastrointestinal cancers prior to age 20 years¹⁸. There is only one report in the literature of a preadolescent with gastrointestinal cancer in PJS, and in this case the patient had colon cancer¹⁹.

The absence of such early onset small bowel cancers in the literature raises the question of whether our patient's specific *STK11* mutation is unique and could have a stronger association with early onset cancer. This specific splice site mutation has been reported in two other patients with PJS both of which were familial¹³. In one of these patients a family history of colon cancer was reported, although the proband did not have cancer¹³. The age of these patients at the time of the study was not reported as it focused on identifying novel mutations. Clearly further studies would be needed to provide evidence of a unique association between this specific mutation and age of onset of cancer. Currently, the genotype-phenotype relationship in PJS suggests that more severe mutations such as deletions may predispose to an earlier age of cancer than missense mutations⁸. At present the genotype does not affect the screening guidelines for patients with PJS. Another possibility to explain a severe phenotype in an otherwise monogenic disease like PJS would be the presence of modifiers. However, there are no other known loci that affect or influence PJS and a much larger study would be required to ascertain modifiers of cancer risk in patients with *STK11* mutations.

Given the extremely high lifetime relative risk of cancer in PJS including small intestinal malignancy screening guidelines are important to assist clinicians in caring for these patients. Screening and surveillance guidelines for gastrointestinal tumors in PJS are available¹⁰. For pediatric patients however, regular screening is not uniform and its purpose is to avoid urgent laparotomy rather than screen for malignancy. Current recommendations call for upper and lower endoscopy at age 8 years in patients with PJS, and then at age 18 years followed by every 2-3 years¹⁰. Screening from 8 years to 18 years with barium contrast enema has been proposed but has not been adopted. The recommendation for the initial screening at 8 years of age in asymptomatic cases of PJS is based on a review of 51 cases of PJS where 30% of the patients had already required a laparotomy by 10 years of age¹². Of the total laparotomies reported in the review 70% of the initial laparotomies were performed urgently for intestinal obstruction mainly due to presence of small bowel polyps. Based on our case and the other case of a child with PJS and gastrointestinal cancer (Saranritichai et al 2009), we propose that guideline for cancer screening in this age group are called for. Capsule endoscopy allows the unique advantages of a full survey of the GI tract and does not have the radiation risks of barium studies. A screening program involving capsule endoscopy every 2 years in patients with PJS between ages 8 and 18 years would be reasonable and could be studied for efficacy. Children with PJS are also at risk for intestinal obstruction such that patients and parents should be aware of the need for prompt medical attention if acute abdominal pain develops. Our case represents the earliest reported case of small bowel cancer in PJS at age 13 years and suggests that between ages 8 years and 18

years, there is a certain risk of malignancy which could be screened for using semi-annual capsule endoscopy in adolescent patients with PJS.²⁰.

Acknowledgments

This work was supported by 5R01CA138836 to SEP. RSC is a St. Baldrick's Foundation Fellow for Childhood Cancer Research. MFW received support from 1 K08 NS076547-01.

LITERATURE CITED

1. McGarrity TJ, Amos C. Peutz-Jeghers syndrome: clinicopathology and molecular alterations. *Cell Mol Life Sci.* Sep; 2006 63(18):2135–2144. [PubMed: 16952058]
2. Jeghers H, Mc KV, Katz KH. Generalized intestinal polyposis and melanin spots of the oral mucosa, lips and digits; a syndrome of diagnostic significance. *N Engl J Med.* Dec 22.1949 241(25):993. illust; passim. [PubMed: 15399020]
3. Hemminki A, Markie D, Tomlinson I, et al. A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. *Nature.* Jan 8; 1998 391(6663):184–187. [PubMed: 9428765]
4. Jenne DE, Reimann H, Nezu J, et al. Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase. *Nat Genet.* Jan; 1998 18(1):38–43. [PubMed: 9425897]
5. Aretz S, Stienen D, Uhlhaas S, et al. High proportion of large genomic STK11 deletions in Peutz-Jeghers syndrome. *Hum Mutat.* Dec; 2005 26(6):513–519. [PubMed: 16287113]
6. Chow E, Meldrum CJ, Crooks R, Macrae F, Spigelman AD, Scott RJ. An updated mutation spectrum in an Australian series of PJS patients provides further evidence for only one gene locus. *Clin Genet.* Nov; 2006 70(5):409–414. [PubMed: 17026623]
7. Papp J, Kovacs ME, Solyom S, Kasler M, Borresen-Dale AL, Olah E. High prevalence of germline STK11 mutations in Hungarian Peutz-Jeghers Syndrome patients. *BMC Med Genet.* 2010; 11:169. [PubMed: 21118512]
8. Amos CI, Keitheri-Cheteri MB, Sabripour M, et al. Genotype-phenotype correlations in Peutz-Jeghers syndrome. *J Med Genet.* May; 2004 41(5):327–333. [PubMed: 15121768]
9. Wei C, Amos CI, Zhang N, Zhu J, Wang X, Frazier ML. Chemopreventive efficacy of rapamycin on Peutz-Jeghers syndrome in a mouse model. *Cancer Lett.* May 18; 2009 277(2):149–154. [PubMed: 19147279]
10. Giardiello FM, Trimbath JD. Peutz-Jeghers syndrome and management recommendations. *Clin Gastroenterol Hepatol.* Apr; 2006 4(4):408–415. [PubMed: 16616343]
11. Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. *Gastroenterology.* Dec; 2000 119(6):1447–1453. [PubMed: 11113065]
12. Hinds R, Philp C, Hyer W, Fell JM. Complications of childhood Peutz-Jeghers syndrome: implications for pediatric screening. *J Pediatr Gastroenterol Nutr.* Aug; 2004 39(2):219–220. [PubMed: 15269641]
13. Ylikorkala A, Avizienyte E, Tomlinson IP, et al. Mutations and impaired function of LKB1 in familial and non-familial Peutz-Jeghers syndrome and a sporadic testicular cancer. *Hum Mol Genet.* Jan; 1999 8(1):45–51. [PubMed: 9887330]
14. Blumer SL, Anupindi SA, Adamson PC, et al. Sporadic adenocarcinoma of the colon in children: case series and review of the literature. *J Pediatr Hematol Oncol.* May; 2012 34(4):e137–141. [PubMed: 22469946]
15. Tankel JW, Galasko CS. Adenocarcinoma of small bowel in 12-year-old girl. *J R Soc Med.* Aug; 1984 77(8):693–694. [PubMed: 6481744]
16. Lim W, Olschwang S, Keller JJ, et al. Relative frequency and morphology of cancers in STK11 mutation carriers. *Gastroenterology.* Jun; 2004 126(7):1788–1794. [PubMed: 15188174]
17. Choi HS, Park YJ, Youk EG, et al. Clinical characteristics of Peutz-Jeghers syndrome in Korean polyposis patients. *Int J Colorectal Dis.* Feb; 2000 15(1):35–38. [PubMed: 10766089]
18. Hearle N, Schumacher V, Menko FH, et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. *Clin Cancer Res.* May 15; 2006 12(10):3209–3215. [PubMed: 16707622]

19. Saranrittichai S. Peutz-jeghers syndrome and colon cancer in a 10-year-old girl; implications for when and how to start screening? *Asian Pac J Cancer Prev.* Jan-Mar;2008 9(1):159–161. [PubMed: 18439097]
20. Ohmiya N, Nakamura M, Takenaka H, et al. Management of small-bowel polyps in Peutz-Jeghers syndrome by using enteroclysis, double-balloon enteroscopy, and videocapsule endoscopy. *Gastrointest Endosc.* Dec; 72(6):1209–1216. [PubMed: 20970791]

Figure 1.

- A. Computed Tomography (CT) scan of the abdomen and pelvis at the level of the sacral spine showing a U-shaped mass in the pelvis indicated by the arrow.
- B. CT scan at the level of the lumbar spine showing the U-shaped mass with a calcification indicated by the arrow.
- C. Digital photograph of the labial mucosa of the patient revealing the presence of hyperpigmented macules which include some extending beyond the vermilion border.
- D. Digital photograph of the palmar surface of the patient revealing the presence of hyperpigmented macules on the digits
- E. Abdominal Ultrasound showing a complex fluid filled structure which contains within it fluid filled loops of bowel. These findings were diagnostic of a lead-point intussusception.

Figure 2. Hamartomatous Polyp in Intussusception in PJS

A. Gross specimen of resected small bowel demonstrating intussusception.

B. Opened small bowel resection revealing gross appearance of polyps, indicated by circles

C & D. A hamartomatous polyp from the small bowel resection with both gross (C) and histologic (D) cross-sections demonstrating extension of the smooth muscle layer from the muscularis propria into the core of the polyp, characteristic of a hamartomatous polyp.

Figure 3. Mucinous Adenocarcinoma Arising From Hamartomatous Polyp in PJS

A & B: Gross (A) and histologic (B) appearance of hamartomatous polyp with invasive mucinous adenocarcinoma.

C: Dysplasia of small bowel mucosa with a hamartomatous polyp organized into a glandular pattern

D. Invasive mucinous adenocarcinoma from a hamartomatous polyp with invasion of the submucosa, and through the muscularis propria

E. Invasive mucinous adenocarcinoma from a hamartomatous polyp with invasion of the small bowel serosa.