Familial Cancer (2011) 10:463–468
DOI 10.1007/s10689-011-9438-x

Case studies in the diagnosis and management of Peutz-Jeghers syndrome

Douglas Riegert-Johnson · Maegan Roberts · Ferga C. Gleeson · Murli Krishna · Lisa Boardman

Published online: 19 April 2011

Abstract Peutz-Jeghers syndrome (PJS) is a rare genetic disorder characterized by melanotic macules, gastrointestinal polyps and increased cancer risks. We discuss several common scenarios encountered in the diagnosis and management of PJS patients. If the diagnosis is unclear, all pathological material should be re-evaluated by an expert gastrointestinal pathologist. The PJS discussion email listserve (patient managed) and the peutz-jeghers.com, geneclinics.org, stk11.com websites are useful resources for patients. Cancer surveillance is accepted as a method to increase survival for PJS patients, thus all PJS patients should be prescribed an individualized surveillance plan based on personal and family history as well as available health care resources while taking into consideration the preferences of the patient. Several recent incremental improvements in PJS care have been made including the use of magnetic resonance enterography (MRE) and double balloon endoscopy (DBE). MRE combines cancer and small intestinal polyp surveillance, which previously had required two or more separate tests. How and when to perform pancreatic cancer surveillance continues to be an unclear area in the management of PJS patients. Endoscopic ultrasound (EUS) is probably the most sensitive investigation for pancreatic cancer detection at an early stage when cure may be possible. However, EUS is limited by variability and false positive results. Female patients with PJS are at risk for two rare cancers that require regular surveillance, adenoma malignum and ovarian sex cord tumors with annular tubules.

Keywords Peutz-Jeghers syndrome · Pancreatic cancer · Adenoma malignum · Sex cord tumors · Magnetic resonance enterography

D. Riegert-Johnson (✉) · M. Roberts · M. Krishna
Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA
e-mail: riegertjohnson.douglas@mayo.edu

M. Roberts
e-mail: roberts.maegan@mayo.edu

M. Krishna
e-mail: krishna.murli@mayo.edu

F. C. Gleeson · L. Boardman
Mayo Clinic, Rochester, MN, USA
e-mail: gleeson.ferga@mayo.edu

L. Boardman
e-mail: boardman.lisa@mayo.edu

Text

Peutz-Jeghers syndrome (PJS) is characterized by melanotic macules, hamartomatous gastrointestinal polyps, an increased risk of cancer and germline mutations in the *LKB1* gene. The first patients now thought to have had PJS were a pair of identical twins reported in 1895 [1]. Through the reports by Peutz and later Jeghers et al. the cardinal features of PJS were characterized [2, 3].

Several review papers on PJS associated cancer risks and cancer surveillance have been published [4, 5]. Latchford and Phillips review the state of the art surveillance for PJS gastrointestinal tract cancers elsewhere in this issue. In this paper, several common scenarios that are often encountered when caring for PJS patients are presented and discussed. Details of the scenarios have been changed to protect patients' confidentiality.

Scenario #1

Diagnosing PJS A 45 year-old woman presented for medical genetics evaluation. Between the ages of 20 and

30 years, the patient had nasal polyps and several large colon polyps removed. At 43 years-old, she was diagnosed with jejunal adenocarcinoma (T1N0). Upper endoscopy following surgery showed several stomach and small bowel polyps. A genetic test for familial adenomatous polyposis (*APC* gene) was negative. There was no family history of cancer.

On physical examination, there was a single melanotic macule on the buccal mucosa. There were no melanotic macules on the lips or elsewhere. The patient underwent another upper endoscopy and several small bowel polyps were removed. These polyps had typical microscopic features of hamartomatous PJS polyps with polypoid, hyperplastic mucosa and bands of arborizing smooth muscle (Fig. 1). The original pathology report for the jejunal adenocarcinoma was retrieved and described arborizing smooth muscle tissue but made no mention of PJS.

Personal and family history, physical examination and pathological interpretation are all crucial components in the diagnosis of PJS. Patients should be asked and examined closely regarding melanotic macules. Almost all PJS patients have or have had melanotic macules on their lips; only a few patients have been reported without them. For a further discussion of disorders of oral pigmentation, please see the paper by Stratakis and others in this issue. The "spots" fade during puberty and may be very subtle or absent in adult patients. When examining for melanotic macules one should look not only at the lips, but also the buccal mucosa, eyelids, around the eyes and ears, along the hairline, on tips of toes and fingers and in the groin region. The patient's combination of characteristic melanotic macules and arborizing smooth muscle pathology meet the diagnostic criteria for PJS (Table 1). Genetic testing later confirmed the clinical diagnosis of PJS with identification of a mutation in *LKB1*.

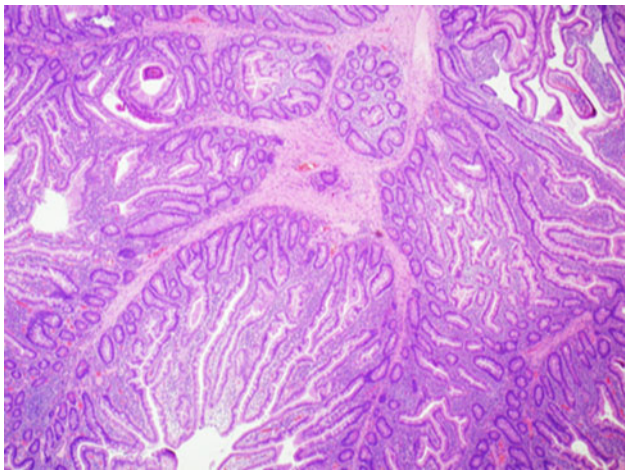

Fig. 1 Photomicroscopy of a harmatomatous polyp from a patient with Peutz-Jeghers syndrome, characterized by hyperplastic epithelium and arborizing bands of smooth muscle (hematoxylin and eosin stain, magnification ×40)

About 15% of patients with PJS have nasal polyps [6]. They are often an overlooked feature of PJS, although they were included in the original description by Peutz ("Very remarkable case of familial polyposis of mucous membrane of intestinal tract and nasopharynx accompanied by peculiar pigmentations of skin and mucous membrane"[2]).

The pathological description of smooth muscle in small intestine polyps is highly sensitive and specific for the disease. There are only a few cases reported where PJS type polyps were seen in patients without PJS [7]. In cases where the diagnosis is unclear, re-evaluation of all pathological material by a gastrointestinal pathologist should be routine. In a study of patients with unexplained hamartomatous and hyperplastic polyposis, review by a gastrointestinal pathologist made the diagnosis in most cases [8].

PJS polyps are rarely seen by pathologists in common clinical practice, and may therefore not be easily recognized. Even if seen, as in this case, the connection to PJS may not be made. For these reasons, when a PJS patient, or suspected PJS patient, has polyps removed, the pathologist should be informed.

Summary A comprehensive approach is needed in the diagnosis of PJS.

Scenario #2

New patient diagnosis The patient discussed above has just received a diagnosis of PJS.

Healthcare providers should be mindful that the diagnosis of PJS is a milestone in the life of any individual and should be handled with the appropriate sensitivity. If the patient is receptive, we recommend the genetics, natural history, and treatment of PJS be reviewed. An individual management plan should be formulated including referral to a genetic counselor. Even though it may not be apparent, most patients benefit from seeing a genetic counselor for a detailed review of the genetics and genetic counseling. PJS patients are at an increased risk for lung cancer and smoking probably increases this risk further. Therefore, nicotine dependence counseling should be included in the management plan of PJS patients who smoke. Online PJS resources can be invaluable for patients (Box 1).

Patients, and especially parents of young PJS patients, are understandably very concerned about the impact of PJS on long-term survival and psychological well being. There is no current, high quality, data on the survival of PJS patients. The available data comes from patients studied over many decades before the recent dramatic improvements in PJS care. The most recent report on PJS survival

Table 1 Diagnostic criteria for Peutz-Jeghers syndrome

Source	Criteria
Mayo Clinic [26]	In patients *without* a family history of PJS, a diagnosis of PJS is made if EITHER of the following are present:
	characteristic melanotic macules and one or more intestinal polyps with PJS-type histology, or
	two intestinal polyps with PJS-type histology.
	In patients *with* family history of PJS in a sibling or child, a diagnosis of PJS is made if ANY of the following are present:
	characteristic melanotic macules, or
	one or more intestinal polyps with PJS-type histology, or
	an *LKB1* mutation.
World Health Organization (2000) [27]	In patients *without* a family history of PJS, a diagnosis of PJS is made if there are:
	three or more histologically confirmed PJS polyps, or
	any number of PJS polyps and characteristic, prominent, PJS mucocutaneous pigmentation
	A diagnosis of PJS can be made in patients *with* a family history of PJS if there are:
	any number of PJS polyps, or
	characteristic, prominent, PJS mucocutaneous pigmentation
Tomlinson and Houston [28]	A diagnosis of PJS can be made if there are:
	two or more intestinal polyps with PJS-type histology, or
	one intestinal polyp with PJS-type histology with either typical melanotic macules, or a family history of PJS and characteristic melanotic macules

Three criteria for the diagnosis of Peutz-Jeghers syndrome (PJS). As all three are similarly based on PJS melanotic macules and intestinal polyps, it would be expected most patients would be diagnosed (or not diagnosed) with PJS regardless of which criteria were used. The WHO criteria makes the point of stating the PJS pigmentation should be "prominent" as perioral pigmentation is common in the general population. The authors (Mayo Clinic) have found that PJS pigmentation often fades after puberty and is sometimes very faint or even absent in adults and therefore have not included that in their criteria. The Mayo criteria also differs from the World Health Organization (WHO) criteria by including *LKB1* mutation testing. PJS = Peutz-Jeghers syndrome

Box 1 Online Peutz-Jeghers syndrome (PJS) resources

A valuable resource for PJS patients is the patient managed PJS discussion list serve hosted by the Association of Cancer Online Resources (ACOR). Archives and subscription information are available at http://listserv.acor.org/archives/pjs.html. Through this list serve, PJS patients from around the world communicate and support one another. Patient meetings are also announced on the list serve. United States PJS patient meetings occurred in 2009 (Destin, Florida) and 2010 (San Francisco, California). The 2011 meeting is scheduled to take place in Aurora, Colorado. Several websites are also useful including peutz-jeghers.com, geneclinics.org and stk11.com

studied 54 patients seen at Mayo Clinic from 1950 to 2002. The median age at death was 51 years [9].

Study results are mixed on the psychological impact of PJS [10, 11]. One study showed PJS patients suffer from mild depression but physically are not impacted by their condition. In another, PJS patients had similar levels of depression and anxiety as seen in the general population, but did have lower general health perception and more limitations due to emotional problems.

Summary For each patient with PJS a comprehensive, personalized patient care plan should be implemented.

Scenario #3

Pancreatic cancer surveillance A 40 year-old woman with PJS is referred for pancreatic cancer screening using endoscopic ultrasound (EUS). She recently had a normal abdominal computed tomography (CT) scan with and without intravenous contrast.

Patients with PJS are at increased risk for pancreatic cancer. The most current and complete data on cancer risk in PJS patients (2006) is from a multicenter collaborative series of 416 PJS patients [12]. The cumulative risks for pancreatic cancer were 3% at 40 years, 5% at 50 years, 7% at 60 years, and 11% at 70 years. By comparison, the population risk at 70 years is 0.5%.

Pancreatic cancer has the worst prognosis of any of the PJS-associated cancers. Less than 5% of general population pancreatic cancer patients are long-term survivors (>5 years). No PJS patient has been reported to be a long-term survivor of pancreatic cancer. Therefore, early detection and treatment of pancreatic cancer is of great interest to PJS patients and physicians treating PJS patients. However, the unfortunate fact is that all pancreatic cancer surveillance

investigations have significant limitations. It is unclear if any one of them, or any combination of them, could decrease pancreatic cancer morbidity and mortality in PJS patients.

Two studies of the effectiveness of pancreatic cancer screening in PJS or similar populations have been published. A Markov model analysis studied surveillance strategies for patients with hereditary pancreatic cancer [13]. Evaluated approaches included "do nothing," total pancreatectomy, endoscopic ultrasound (EUS), and EUS with fine needle aspiration (FNA). The "do nothing" approach provided the longest number of years of life. The second study, a review and cost-effectiveness evaluation of pancreatic cancer screening specifically in PJS, determined that EUS screening was not cost-effective and recommended that it only be performed in a research setting [14].

EUS is probably the most sensitive test in detecting precancerous and cancerous pancreas lesions that could potentially be cured by surgery. It is more sensitive than the CT scan the patient recently had, however, EUS is limited by intra- and inter-observer variability for findings other than cysts [15] and false positive test results. Highly sensitive cancer screening tests, such as EUS, are plagued by false positive results when used in populations that are unlikely to have cancer. EUS testing may identify an abnormality (example: a cyst) that may or may not indicate a very early pancreatic cancer. Once a PJS patient is found to have an abnormal EUS finding suggesting the possibility of pancreatic cancer, many patients will opt for pancreatic surgery. However, in some of these patients, pancreatic cancer will not be found in the surgical specimen [16].

Based on the fact that cancer surveillance is needed for all intra-abdominal organs, including the pancreas, the Mayo Clinic and other groups recommend an annual abdominal MRI (magnetic resonance imaging). Annual abdominal MRI with an added enterography protocol, magnetic resonance enterography (MRE), offers "a one stop shop". MRE surveys all abdominal organs including the pancreas and also detects small intestine polyps. What had previously been performed with three investigations (EUS, computated tomography (CT), and capsule endoscopy) in many centers can now be performed with one. MRE has the added benefit of not being associated with radiation exposure, as CT is, and the possibility of increased cancer risk from that radiation exposure [16, 17]. MRE is further discussed in Scenario #4.

As most PJS patients will have an annual MRE, the question is whether or not to add EUS to their list of investigations. The authors review the pancreatic cancer risk associated with PJS and the available strategies, including EUS, with patients. In the authors' collective experience, patients are undecided on whether or not to add EUS to their cancer surveillance protocol. This particular patient elected to have an EUS; the results were normal.

Summary How and when to perform pancreatic cancer surveillance continues to be an unclear area in the management of PJS patients.

Scenario #4

Small intestine polyp tests A 25 year-old male PJS patient presents with iron deficiency anemia and abdominal pain. The abdominal pain has been present for 3 months and is located in the right upper quadrant of the abdomen. He describes it as sharp and it lasts up to 3 h. Five years ago he had an upper endoscopy, colonoscopy, and barium enterography ("small bowel series") that were normal.

The patient's history is consistent with an internment small intestine polyp intussusception. The pain of intussusception is intermittent, consistently occurs in the same general location and often reported as "attacks" lasting a few hours. Iron deficiency anemia is often associated with intussusception. For confirmation of the clinical diagnosis of intussusception, the authors would order magnetic resonance enterography (MRE). Where MRE is not available, capsule endoscopy is an acceptable alternative. A recent study compared MRE and capsule endoscopy for small bowel polyp detection in 19 PJS patients. MRE did have less inter-observer variability than capsule endoscopy and detected more polyps than capsule endoscopy, however the difference was not statistically significant [18].

Patients with pacemakers can not have MRE and other implantable hardware may or may not be a contraindication to MRE. Patients with claustrophobia can usually still have MRE, most needing only sedation with an oral benzodiazepine. The procedure for MRE is different than other radiology tests and it maybe useful to review the procedure with the patient (Box 2).

MRE was performed on the patient above. A 4 cm ileal polyp was identified (Fig. 2) and later removed by lower double balloon endoscopy.

Summary MRE should be the first small bowel polyp test considered for the PJS patient.

Scenario #5

Gynecological cancer risks and surveillance A 25 year-old female PJS patient comes to arrange surveillance. She is concerned about the risk for adenoma malignum (ADM). Her aunt, who also had PJS, died of metastatic breast cancer and ADM at age 65. The patient's only manifestations of PJS to date are melanotic macules and an intussusception of a small intestinal polyp at age 16 requiring surgery.

Female PJS patients are at increased risk for common gynecological cancers and two rare gynecological cancers,

Box 2 Magnetic resonance enterography (MRE) protocol

The preparation described here is for individuals with Peutz-Jeghers syndrome who have MRE with abdominal and pelvic MR. Patients should have nothing by mouth other than water and their medications for 6 h prior to arriving at the imaging center. Before arriving at the imaging center patients, will need to use a phosphosoda enema. At the imaging center, patients will be asked to rapidly drink a large amount of oral contrast. At Mayo Clinic Florida, patients drink three 450 ml bottles of VoLumen brand oral contrast followed by water. Most PJS patients have had many barium studies and developed a strong aversion to the chalky taste of barium. Fortunately, MRE oral contrast does not have a strong taste and is well tolerated

After ingesting the oral contrast, patients will be scanned for about 1 h, sometimes longer. For most MR scans patients are positioned on their back (supine), however, for MRE patients are usually positioned on their abdomen (prone). During scanning, intravenous glucagon and a contrast agent are given. Glucagon paralyzes the small intestine and without glucagon the normal peristaltic movement of the small intestine would prevent obtaining high quality MRE images. Patients usually have diarrhea after the procedure from the oral contrast

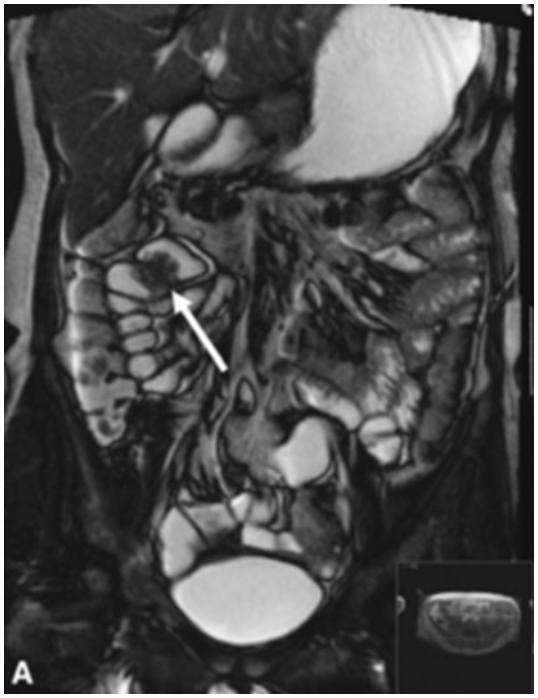

Fig. 2 An approximately 4 cm ileal polyp in a Peutz-Jeghers syndrome patient as seen by magnetic resonance enterography (*arrow*). Image reproduced from Postgate et al. with permission [29]

adenoma malignum (ADM) and sex cord tumor with annular tubules (SCTATs). ADM is a highly differentiated adenocarcinoma of the endocervical glands. The number of female PJS patients who develop ADM is low (<5%). Several large case series of PJS patients have not reported a single case [19]. About 10% of patients with ADM have PJS [20].

Patients presenting with ADM often report a history of watery vaginal discharge and/or vaginal bleeding. Establishing the diagnosis of ADM can be difficult. On examination the cervix has alternatively been described as being normal, having a firm or nodular appearance, or resembling a polypoid mass [21]. Papanicolaou (Pap) cervical smear or cervical biopsy can be diagnostic in some but not all cases. Imaging studies show multiple cervical cysts [21]. Most PJS protocols recommend surveillance for ADM by yearly gynecologic exam with Pap smear and pelvic imaging generally by transvaginal ultrasound [5]. Patients with ADM should be referred to a gynecological oncologist for surgery and possible systemic treatment.

The authors estimate about 10% of female PJS patients will develop SCTATs that require surgery. About one-third of patients with SCTATs have PJS [22]. PJS-associated SCTATs are bilateral, multifocal, often microscopic, and contain focal calcifications. In contrast, sporadic SCTATs are large and unilateral. PJS-associated SCTATs have a low malignant potential and generally a good prognosis. Only three cases of malignant SCTATs have been reported in PJS patients [23–25]. PJS patients with SCTATs often present with an asymptomatic adnexal cyst or mass identified by one of the cancer surveillance tests discussed above. SCTATs sometimes produce estrogen, causing precocious puberty in prepubescent female patients. A conservative approach to SCTATs with preservation of fertility and avoidance of surgical menopause is recommended. PJS patients with known or suspected SCTATs should be referred to both a gynecological oncologist and, if of reproductive age, a reproductive endocrinologist.

Summary Although PJS is considered primarily a gastrointestinal disease, gynecological cancer surveillance should not be neglected.

Conclusion

These case studies illustrate the complex and multi-system nature of PJS. We recommend a care plan with both medical and non-medical support. Medical support should include a "medical home" with a physician and other care providers such genetic counselors experienced with PJS to coordinate cancer surveillance and, if needed, cancer treatments. For non-medical support, patients should be put in contact with other PJS patients and social services.

Conflict of interest None.

References

1. Connor J (1895) Aesculapian society of London. Lancet 2:1169
2. Peutz J (1921) Very remarkable case of familial polyposis of mucous membrane of intestinal tract and nasopharynx accompanied by peculiar pigmentations of skin and mucous membrane. Nederl Maandschr Geneesk 10:134–146
3. Jeghers H, McKusick V, Katz KH (1949) Generalized intestinal polyposis and melanin spots of the oral mucosa, lips and digits; a syndrome of diagnostic significance. N Engl J Med 241(25):993
4. Beggs AD, Latchford AR, Vasen HF et al (2010) Peutz-Jeghers syndrome: a systematic review and recommendations for management. Gut 59(7):975–986
5. van Lier MG, Wagner A, Mathus-Vliegen EM, Kuipers EJ, Steyerberg EW, van Leerdam ME (2010) High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. Am J Gastroenterol 105(6):1258–1264 author reply 1265
6. de Leng WW, Westerman AM, Weterman MA et al (2007) Nasal polyposis in Peutz-Jeghers syndrome: a distinct histopathological and molecular genetic entity. J Clin Pathol 60(4):392–396
7. Oncel M, Remzi FH, Church JM, Goldblum JR, Zutshi M, Fazio VW (2003) Course and follow-up of solitary Peutz-Jeghers polyps: a case series. Int J Colorectal Dis 18(1):33–35
8. Sweet K, Willis J, Zhou XP et al (2005) Molecular classification of patients with unexplained hamartomatous and hyperplastic polyposis. JAMA 294(19):2465–2473
9. You YN, Wolff BG, Boardman LA, Riegert-Johnson DL, Qin R (2010) Peutz-Jeghers syndrome: a study of long-term surgical morbidity and causes of mortality. Fam Cancer
10. van Lier MG, Mathus-Vliegen EM, van Leerdam ME et al (2010) Quality of life and psychological distress in patients with Peutz-Jeghers syndrome. Clin Genet 78(3):219–226
11. Woo A, Sadana A, Mauger DT, Baker MJ, Berk T, McGarrity TJ (2009) Psychosocial impact of Peutz-Jeghers syndrome. Fam Cancer 8(1):59–65
12. Hearle N, Schumacher V, Menko FH et al (2006) Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. Clin Cancer Res 12(10):3209–3215
13. Rubenstein JH, Scheiman JM, Anderson MA (2007) A clinical and economic evaluation of endoscopic ultrasound for patients at risk for familial pancreatic adenocarcinoma. Pancreatology 7(5–6):514–525
14. Latchford A, Greenhalf W, Vitone LJ, Neoptolemos JP, Lancaster GA, Phillips RK (2006) Peutz-Jeghers syndrome and screening for pancreatic cancer. Br J Surg 93(12):1446–1455
15. Topazian M, Enders F, Kimmey M et al (2007) Interobserver agreement for EUS findings in familial pancreatic-cancer kindreds. Gastrointest Endosc 66(1):62–67
16. Canto MI, Goggins M, Yeo CJ et al (2004) Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. Clin Gastroenterol Hepatol 2(7):606–621
17. Smith-Bindman R, Lipson J, Marcus R et al (2009) Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. Arch Intern Med 169(22):2078–2086
18. Gupta A, Postgate AJ, Burling D et al (2010) A prospective study of MR enterography versus capsule endoscopy for the surveillance of adult patients with Peutz-Jeghers syndrome. AJR Am J Roentgenol 195(1):108–116
19. Spigelman AD, Murday V, Phillips RK (1989) Cancer and the Peutz-Jeghers syndrome. Gut 30(11):1588–1590
20. Gilks CB, Young RH, Aguirre P, DeLellis RA, Scully RE (1989) Adenoma malignum (minimal deviation adenocarcinoma) of the uterine cervix. A clinicopathological and immunohistochemical analysis of 26 cases. Am J Surg Pathol 13(9):717–729
21. Tsuruchi N, Tsukamoto N, Kaku T, Kamura T, Nakano H (1994) Adenoma malignum of the uterine cervix detected by imaging methods in a patient with Peutz-Jeghers syndrome. Gynecol Oncol 54(2):232–236
22. Young RH, Scully RE (1982) Ovarian sex cord-stromal tumors: recent progress. Int J Gynecol Pathol 1(1):101–123
23. Lele SM, Sawh RN, Zaharopoulos P et al (2000) Malignant ovarian sex cord tumor with annular tubules in a patient with Peutz-Jeghers syndrome: a case report. Mod Pathol 13(4):466–470
24. Rodu B, Martinez MG Jr (1984) Peutz-Jeghers syndrome and cancer. Oral Surg Oral Med Oral Pathol 58(5):584–588
25. Barker D, Sharma R, McIndoe A et al (2010) An unusual case of sex cord tumor with annular tubules with malignant transformation in a patient with Peutz-Jeghers syndrome. Int J Gynecol Pathol 29(1):27–32
26. Riegert-Johnson DL, Gleeson FC, Westra W, Hefferon T, Wong Kee Song LM, Spurck L, Boardman LA (2010) Peutz-Jeghers syndrome. Cancer Syndromes www.stk11.com
27. Aaltonen LA, Billaud M, Järvinen H, Jass JR, Gruber SB (2000) World health organization classification of tumours, pathology and genetics, tumours of the digestive system. IRAC press, Lyon
28. Tomlinson IP, Houlston RS (1997) Peutz-Jeghers syndrome. J Med Genet 34(12):1007–1011
29. Postgate A, Despott E, Burling D et al (2008) Significant small-bowel lesions detected by alternative diagnostic modalities after negative capsule endoscopy. Gastrointest Endosc 68(6):1209–1214