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AGGRESSIVE COLORECTAL SIGNET RING CELL CARCINOMA ARISING IN PEUTZ-JEGHERS SYNDROME: A RARE CASE OF MISSED SURVEILLANCE WITH SUCCESSFUL MULTIMODAL THERAPY

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ABSTRACT

Introduction: Peutz-Jeghers syndrome (PJS) is a rare hereditary condition characterised by mucocutaneous pigmentation and hamartomatous polyps in the gastrointestinal tract, associated with a significantly increased risk of malignancies, particularly gastrointestinal cancers. Among these, signet ring cell carcinoma (SRCC) of the colon is extremely rare and highly aggressive.

Case description: We report a case of a 36-year-old Vietnamese male with a known history of PJS who presented with left iliac fossa pain. A colonoscopy revealed multiple colonic polyps and a type 3 ulcerated mass in the sigmoid colon; histopathology confirmed SRCC. The patient underwent a laparoscopic colectomy and was diagnosed with stage IIIC (T4aN2bM0) colonic SRCC. He completed twelve cycles of adjuvant FOLFOX4 chemotherapy. Fourteen months post-surgery, he remains disease-free with excellent performance status.

Conclusion: This case illustrates the unpredictable progression of colonic SRCC in patients with PJS, emphasising the need for close periodic surveillance. Accurate diagnosis and timely interventions, including surgery and chemotherapy, are essential for improving outcomes in these high-risk individuals.

KEYWORDS

Peutz-Jeghers syndrome, signet ring cell carcinoma, colorectal cancer, laparoscopic colectomy

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LEARNING POINTS

- People with Peutz-Jeghers syndrome (PJS) have a high risk of gastrointestinal cancers, including rare types such as signet ring cell carcinoma (SRCC).
- Early screenings and regular follow-up are crucial in PJS patients for the timely detection and management of cancerous and precancerous growths, to avoid severe progression.
- For colorectal SRCC in PJS patients, prompt surgery and chemotherapy could lead to positive outcomes.

INTRODUCTION/BACKGROUND

Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant disorder characterised by mucocutaneous pigmentation and multiple hamartomatous polyps throughout the gastrointestinal tract[1]. It is caused by STK11 tumour suppressor gene mutations and is associated with a markedly increased risk of gastrointestinal and extra-gastrointestinal malignancies[2]. Among these, colorectal cancer is one of the most frequently encountered, with affected individuals having a 39% lifetime risk. Despite its distinct clinical presentation, many cases remain underdiagnosed or are identified late due to lapses in surveillance[3]. Signet ring cell carcinoma (SRCC), a rare and aggressive subtype of colorectal cancer, is even more uncommon in the setting of



Figure 1. A-C) Multiple flat, dark brown pigmented macules (1–5 mm) observed on the palms, soles, and face of the patient; D-F) Similar lesions seen on the palms, soles, and face of the patient's brother.

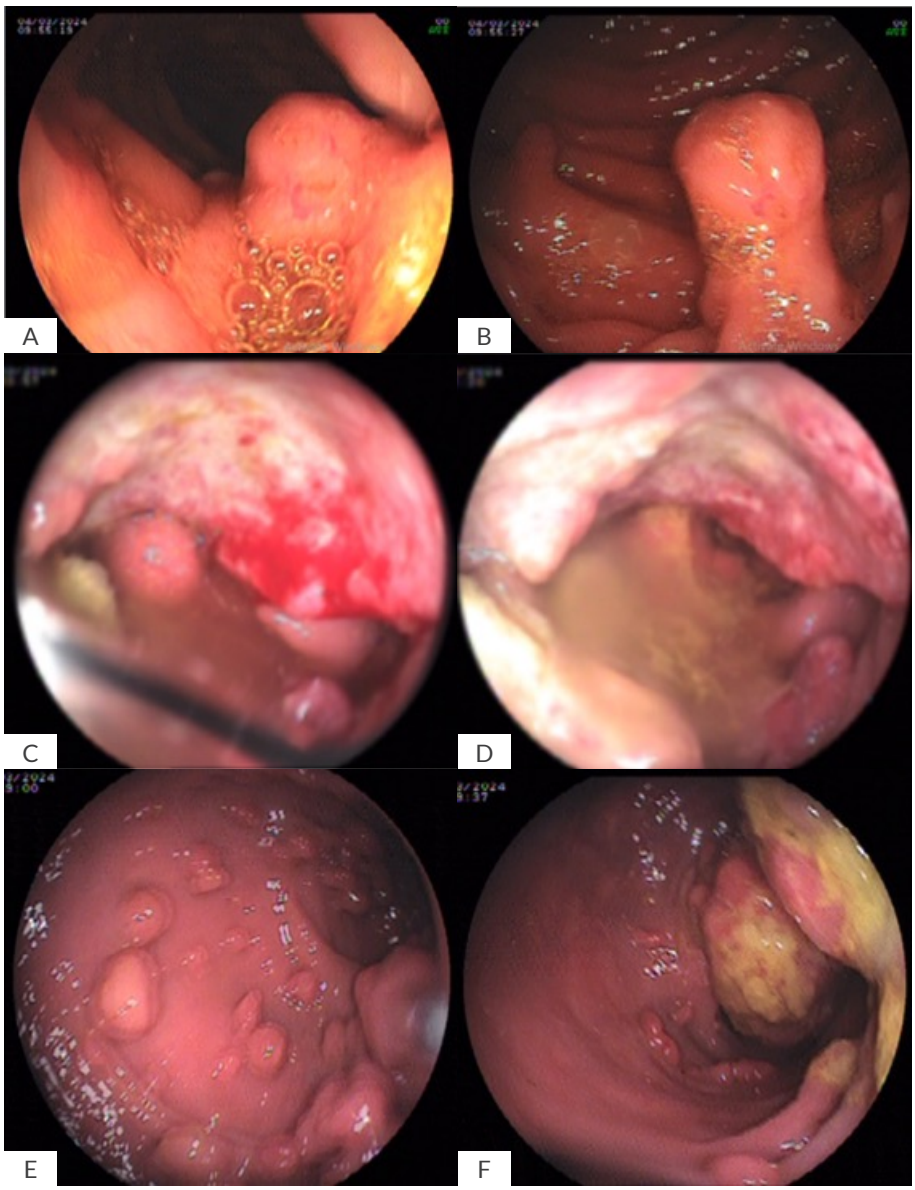


Figure 2. A, B) Upper gastrointestinal endoscopy revealed multiple gastric and duodenal polyps, the largest measuring approximately 1.5 cm with a long stalk; C, D) Colonoscopy showed a type 3 ulcerated mass lesion in the sigmoid colon, measuring approximately 4 cm; E, F) Numerous colorectal polyps of varying sizes were seen throughout the colon, the largest measuring up to 4 cm in diameter.

PJS[4]. This report presents a rare case of sigmoid SRCC in a young Vietnamese male with a known history of PJS who had previously undergone surgery for intussusception. The case emphasises the importance of regular surveillance and highlights the challenges in managing malignancies arising in the context of PJS.

CASE DESCRIPTION

A 36-year-old male patient was admitted to the Oncology Centre (Thai Nguyen Central Hospital, Vietnam) with abdominal pain in the left iliac fossa. For a month the patient had dull abdominal pain, increased pain when defecating, accompanied by loose stools, sometimes mixed with blood and mucus, about 1–2 times a day. In the past, the patient was diagnosed with PJS and treated for intussusception by laparoscopic surgery at the age of 20. When discharged from the hospital, our hospital advised the patient to undergo an endoscopy of the stomach and colon at least once every three years when there were no symptoms, and at least once a year if there were any abnormal digestive symptoms such as abdominal pain or bloody stools. However, from then until this hospitalisation, the patient had not gone to the doctor, although he sometimes felt bloated, had indigestion and occasionally had vague, dull or colicky abdominal pain.

On examination, the patient had pain when pressing the left iliac fossa. Many round oval, irregular black spots, 1 to 7 mm in diameter, which did not fade when pressed, appeared on the skin of the face and around the mouth, hands and feet. These black spots appeared from a young age and gradually increased in number and size. The patient's mother and brother also showed similar pigmented lesions *(Fig. 1)*. In addition, the patient's mother was confirmed to have cervical cancer.

Laboratory tests showed a red blood cell count of 6.72×10^{12}/l, haemoglobin of 13.1 g/dl and a platelet count of 422×10^{9}/l; international normalised ratio of 1.09; carcinoembryonic antigen of 29.8 ng/mL; HBsAg (–), AntiHCV (–), AntiHIV (–).

An upper gastrointestinal endoscopy showed multiple polyps in the stomach and duodenum, the largest measuring approximately 1.5 cm. A colonoscopy showed multiple large pedunculated polyps, the largest of which was 4 cm, accompanied by smaller polyps densely located throughout

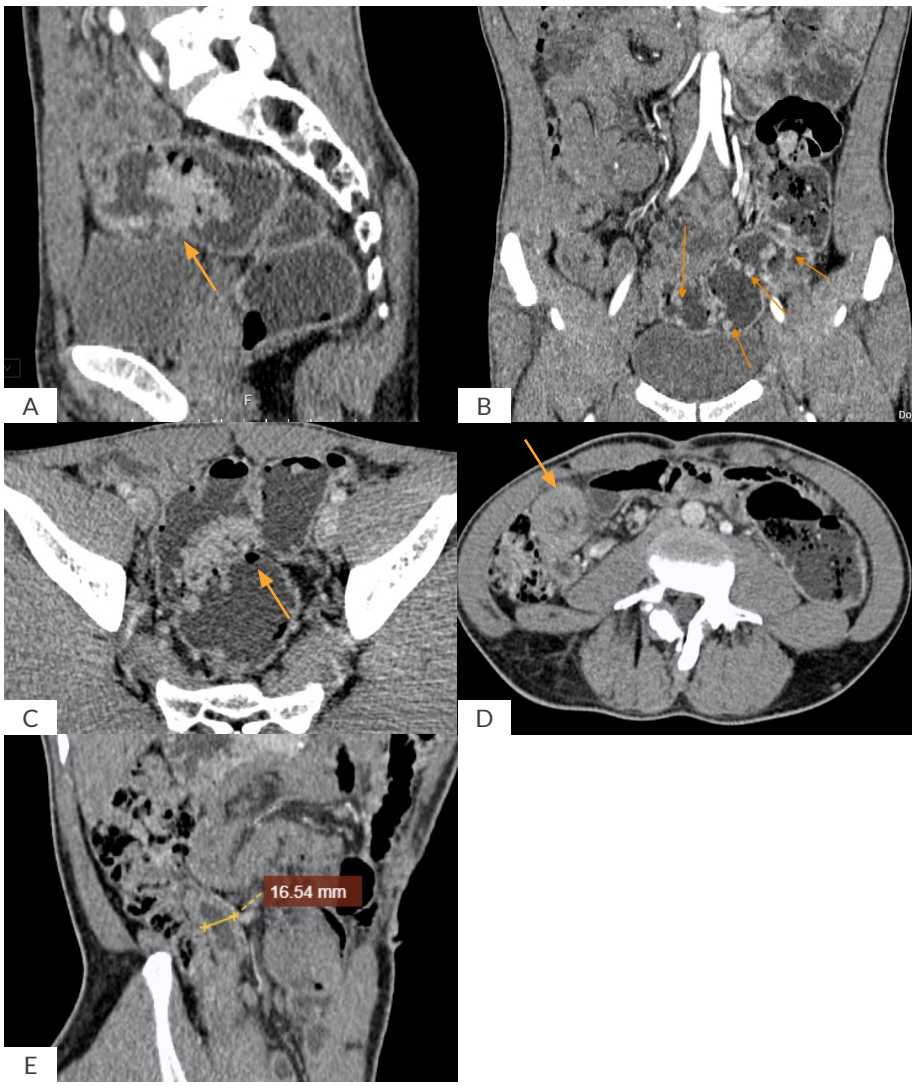


Figure 3. A, C) A sigmoid colon mass with a broad base infiltrates the colon's wall (yellow arrow), homogeneously enhancing it following IV contrast administration. The findings are postoperative confirmed as sigmoid colon cancer; B) Multiple colorectal polyps are detected on CT images with homogeneous enhancement (orange arrow); D) Ileoileal intussusception is seen as the "target" sign in the right lower quadrant region (yellow arrow); E) The appendix is enlarged with a thick wall and filled with fluid. No fat infiltration in the adjacent soft tissue was detected.

the colon. A colonoscopy revealed a type 3 ulcerated mass lesion, suspicious for malignancy in the sigmoid colon, measuring approximately 4 cm, with five biopsy specimens for histopathological examination *(Fig. 2)*. A computed tomography (CT) scan of the abdomen with intravenous contrast showed sigmoid colon cancer, abdominal lymph node metastasis, bilateral flank intussusceptions and an enlarged appendix *(Fig. 3)*. The histopathological examination result was SRCC.

The patient underwent a laparoscopic colectomy. During the operation, the intussusception site was first checked, and the condition of the small intestine was good; there was no evidence of tissue necrosis. The surgeon performed a manual examination of the entire bowel. Multiple tumours of varying sizes were observed along the bowel. The intussusception was resolved by decompression of the affected small intestine. Second, a conventional sigmoid colectomy with lymph node dissection was performed *(Fig. 4)*. The tumour invaded through the visceral peritoneum, and did not adhere to adjacent organs or structures. The histological pathology was SRCC infiltrating the fibrofatty serosa, with 8/18 positive lymph nodes and negative surgical margins. Histologically, the polyps collected in the appendix and sigmoid colon were diagnosed as Peutz-Jeghers polyps *(Fig. 5)*. The patient was diagnosed with stage IIIC T4aN2bM0 SRCC. After surgery, the patient received 12 cycles of adjuvant chemotherapy over six months with FOLFOX4 (5-fluorouracil, leucovorin and oxaliplatin). After six months of adjuvant chemotherapy, the patient no longer had abdominal pain, no blood in the stool, was in good physical condition, gained 3 kg, had a BMI of 21.2, had a surgical scar that had healed well, and had an Eastern Cooperative Oncology Group (ECOG) score of 0. Currently, 14 months after surgery, the patient is still healthy, with no signs of recurrence or disease progression.

DISCUSSION

PJS is a rare autosomal dominant inherited disorder characterised by mucocutaneous pigmentation and hamartomatous polyps in the gastrointestinal tract. Signet ring cell carcinoma of the colon associated with PJS is sporadic, with only a few similar cases reported in the literature *(Table 1)*. It is caused by mutations in the STK11 tumour suppressor gene on chromosome 19p13.3[5]. While the primary clinical features often manifest during childhood or adolescence, PJS is associated with a markedly increased lifetime risk of developing various malignancies – particularly gastrointestinal cancers – including colorectal, pancreatic and gastric cancers[2].

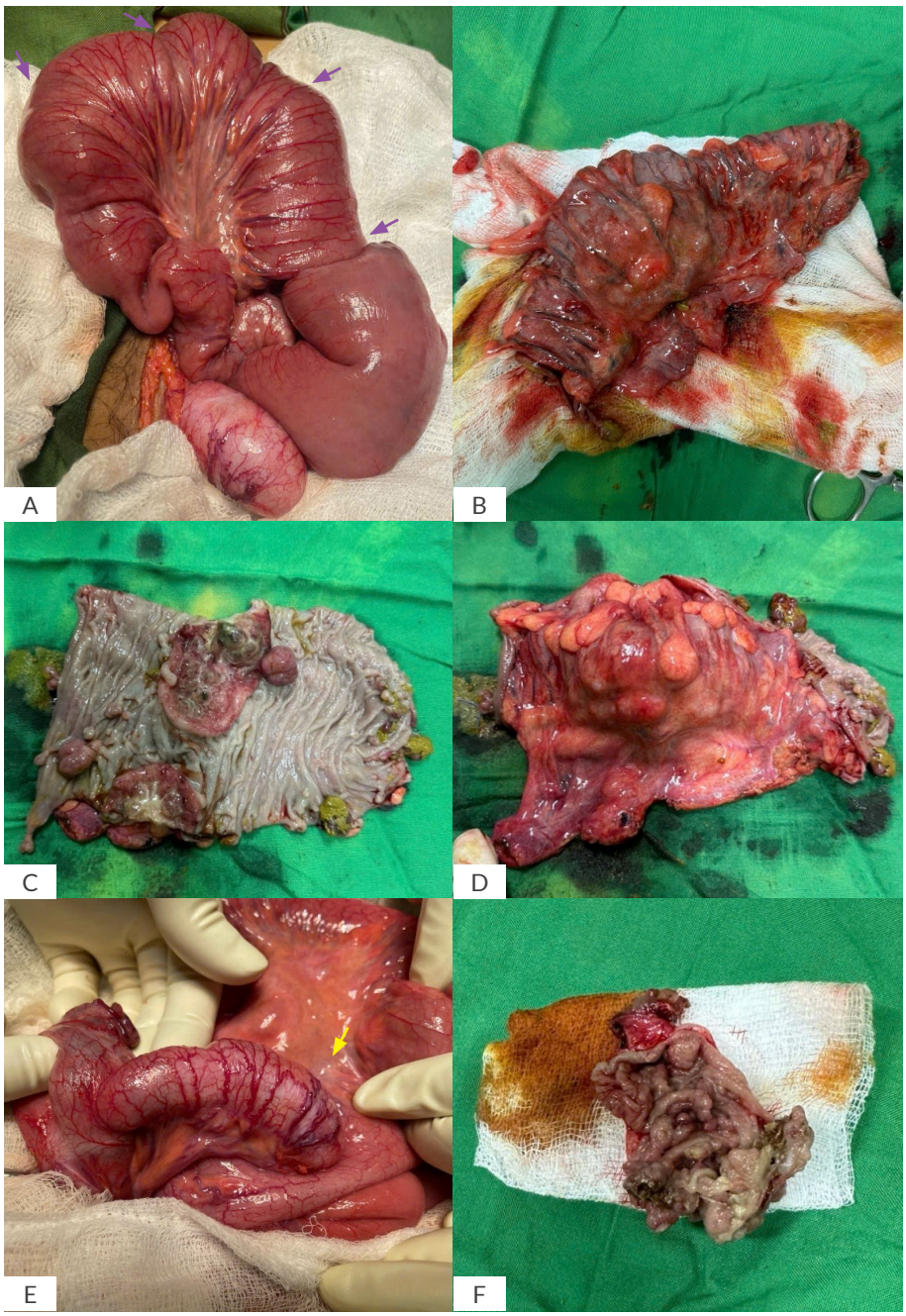


Figure 4. A) Image of intussusception of the small intestine (violet arrow); B-D) The sigmoid colon, which had multiple polyps, was surgically removed through an open procedure; E, F) Image of enlarged appendix (yellow arrow).

This case describes a 36-year-old Vietnamese male with a known history of PJS who developed colorectal SRCC, a rare and aggressive histological subtype of adenocarcinoma. Notably, this patient had undergone laparoscopic surgery for intussusception at the age of 20, a complication commonly associated with large PJS polyps, but did not engage in regular follow-up screening thereafter. This lapse in surveillance is serious, given that early detection through routine endoscopic evaluation is key to cancer prevention in PJS.

Beggs et al.[2] undertook a comprehensive review of the existing literature, drawing on multiple databases, including Ovid MEDLINE (1950–2010), Ovid EMBASE (1980–2010), Ovid OLDMEDLINE, the Cochrane Database of Systematic Reviews, and PubMed. They implemented distinct search strategies utilising the MeSH terms "Peutz-Jeghers syndrome" and "screening". The strength of the evidence was carefully evaluated using the guidelines set out by the North of England Evidence-Based Guidelines Development Project. They recommended that PJS patients perform a baseline colonoscopy and upper gastrointestinal endoscopy at age 8. For individuals with significant polyps detected, these procedures should be repeated every three years. After the age of 50, due to the rapid rise in cancer risk at this age, the frequency should be increased to every 1 to 2 years. However, no evidence supports the benefit of this increased frequency (level of evidence: III, grade of recommendation: C)[2].

Following the above recommendations, our hospital advised the patient to have regular check-ups and an endoscopy to prevent cancer progression. However, because the patient is a farmer, has limited awareness of the disease, lives in the suburbs, does not have the habit of regular medical check-ups, and is still in financial difficulty, when the disease

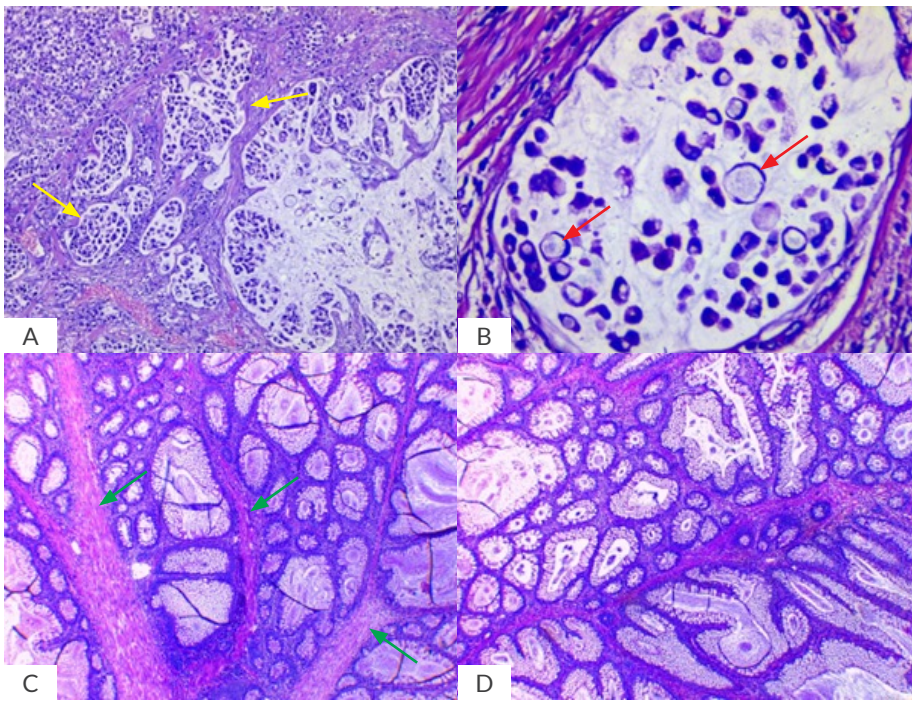


Figure 5. A, B) Signet ring cell carcinoma: Proliferation of signet ring cells with intracellular mucin that displaces nucleus to side; C, D) Peutz-Jeghers polyp: distinctive papillary villous architecture with tree-like arborization of compact smooth muscle bundles and relatively normal overlying epithelium; (red arrow: signet ring cell, yellow arrow: tumor invades stroma, green arrow: tree-like arborization of smooth muscle).

Citation	Sex/age	Initial diagnostic Test	History	Location/type of cancer	Stage at diagnosis	Metastasis	Treatment
Current case	M/36	Colonoscopy	PJS with prior intussusception	Sigmoid/colonic signet cell adenocarcinoma	IIIC (T4aN2bM0)	Regional lymph nodes	Laparoscopic colectomy + FOLFOX4
Remalayam et al.[1]	F/32	Endoscopy, CT	PJS, ovarian mucinous cystadenoma,	Right colon/ colonic signet cell adenocarcinoma	ND	Left Krukenberg ovarian adenocarcinoma	Laparoscopic colectomy + FOLFOX4
Clements et al.[8]	F/43	CT	PJS	Bilateral breast /concomitant breast cancer	Advanced-stage	Ovaries, cervix	Chemotherapy followed by laparotomy with a hysterectomy and oophorectomy
Khan et al.[5]	M/20	Endoscopy	Asthma and attention deficit hyperactive disorder	Hepatic flexure colon/ signet-ring cell adenocarcinoma	IVB (T4N2M1)	Regional lymph nodes, peritoneal carcinomatosis	FOLFOX4 regimen and bevacizumab/ FOLFIRI plus cetuximab
Zheng et al.[7]	M/67	CT, Gastroscopy, Colonoscopy	PJS	Greater omentum, Intestine/ Infiltrating adenocarcinoma	T4bNxM1	Liver, abdominal lymph node	Intussusception reduction, surgery, XELOX chemotherapy
Farraj et al.[6]	M/19	CT, Colonoscopy	Previously healthy	Ascending colon/ signet ring cell adenocarcinoma	IVA (T4a N0 M1)	Peritoneal seeding	Right hemicolectomy, bevacizumab and oxaliplatin

Abbreviations: CT, computed tomography; F, female; M, male; M, metastasis; ND, no data; N, node; PJS, Peutz-Jeghers syndrome; T, tumor.

Table 1. Clinicopathologic features and treatment outcomes of colorectal signet ring cell carcinoma in patients with or without Peutz-Jeghers syndrome: a comparative case summary.

progresses seriously, he is hospitalised for treatment. The test for occult blood cells in the stool at our hospital is not yet covered by insurance and has not been widely deployed to screen patients like this.

The diagnosis of SRCC in this patient is of particular interest due to its rarity in the colon and its association with a poorer prognosis compared to conventional adenocarcinomas. SRCC accounts for less than 1% of all colorectal cancers and is characterised histologically by mucin-producing cells that displace the nucleus to the cell periphery. These tumours are typically more aggressive, present at advanced stages and exhibit lower responsiveness to chemotherapy[6]. In this case, the tumour was classified as stage IIIC (T4aN2bM0), with peritoneal penetration and multiple positive lymph nodes. Despite this, the patient responded well to FOLFOX4 adjuvant chemotherapy and remained disease-free 14 months postoperatively.

The high incidence of malignancy in PJS is well documented. According to a landmark study by Hearle et al., individuals with PJS have a cumulative cancer risk of approximately

93% by age 64, with colorectal cancer representing one of the most common malignancies (39% cumulative risk)[3]. Furthermore, PJS-associated colorectal cancer often arises from adenomatous transformation within hamartomatous polyps or adjacent mucosa undergoing chronic irritation and dysplasia[7]. In this case, Peutz-Jeghers polyps and a background of multiple polyps throughout the colon corroborate this pathogenic sequence.

Surveillance guidelines for PJS recommend initiating colonoscopic screening as early as age 8, with intervals of 2–3 years if polyps are detected, and annual screening in high-risk cases[4]. Upper gastrointestinal endoscopy, small bowel imaging and surveillance for extra-intestinal cancers are also advised. The lapse in follow-up in this patient likely contributed to delayed diagnosis, emphasising the critical need for strict adherence to surveillance protocols. Moreover, family screening and genetic counselling are essential, given the hereditary nature of PJS[8]. The presence of pigmented lesions in the patient's mother and brother, along with the mother's history of cervical cancer, further highlights a likely familial syndrome. However, formal genetic testing was not documented in this case.

Surgical intervention remains the cornerstone of treatment for localised colorectal SRCC. In this patient, a laparoscopic sigmoid colectomy with lymph node dissection was performed, consistent with current oncological principles for advanced colon cancer[9]. The intraoperative finding of multiple tumours and resolved intussusception is consistent with the polyp burden in PJS. Notably, the patient's favourable outcome at 14 months may be partly attributable to complete surgical resection and a robust response to FOLFOX4 chemotherapy. However, longer follow-up is necessary to assess recurrence risk, especially given SRCC's known aggressiveness.

Adjuvant chemotherapy with FOLFOX4 has demonstrated efficacy in stage III colorectal cancer, with studies showing improved disease-free and overall survival. While data specific to SRCC are limited due to its rarity, current National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines recommend adjuvant chemotherapy for stage III disease regardless of histology[10]. The observed clinical benefit in this patient supports the continued use of FOLFOX4 in SRCC, although further studies are warranted to optimise treatment strategies. This case underscores several key clinical considerations. First, regular and lifelong surveillance is indispensable in PJS patients to enable early detection and intervention for malignancies. Second, clinicians must maintain a high index of suspicion for colorectal cancer in patients with PJS presenting with gastrointestinal symptoms, even at a relatively young age. Third, the aggressive nature of SRCC necessitates prompt diagnosis and multimodal treatment. Finally, this case reinforces the importance of genetic counselling and family evaluation, which were not adequately addressed here but represent an essential component of comprehensive care.

CONCLUSION

The development of colorectal SRCC in a young PJS patient illustrates the significant cancer risks inherent with this syndrome and the favourable outcomes achievable with timely surgical and chemotherapeutic intervention. This case also highlights the need for improved patient education, surveillance adherence and the systemic incorporation of genetic services in managing hereditary cancer syndromes.

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