Rectal Adenocarcinoma in Juvenile Polyposis Syndrome: Insights from Two Case Reports

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KEY WORDS: juvenile polyposis syndrome (JPS), rectal adenocarcinoma, rectal cancer, total neoadjuvant therapy

IMAJ 2025; 27: 456–458

Juvenile polyposis syndrome (JPS) is a rare autosomal dominant disorder characterized by hamartomatous polyps throughout the gastrointestinal tract, with an estimated prevalence of 1 in 100,000 individuals. While most cases follow an autosomal dominant inheritance pattern, some are caused by de novo mutations [1].

The age of onset for JPS is typically during childhood or adolescence, with a mean age at diagnosis of 18.5 years [2]. A major concern in JPS is the increased risk of colorectal cancer (CRC), requiring close lifelong surveillance. The cumulative lifetime risk for CRC ranges from 38% to 68%, with a mean age at diagnosis between 34 and 44 years [3].

Although juvenile polyps were initially considered to have low malignant potential, studies have identified two pathways of carcinogenesis in JPS: progression from hamartomatous polyps to adenoma and then to adenocarcinoma or direct transformation of hamartomatous polyps into adenocarcinoma. The management of JPS is tailored to each patient's specific manifestations and clinical presentation. The primary treatment goal is to prevent morbidity associated with gastrointestinal polyps, such as bleeding and intestinal obstruction.

There is currently no curative treatment available. Treatment strategies typically follow two main approaches: endoscopic polypectomy and surgical management. Surgical management is employed in cases with extensive polyps that are not manageable by endoscopic means or in patients presenting with severe or refractory anemia [4].

There is a scarcity of literature on rectal adenocarcinoma in JPS patients. We present two cases of JPS-associated rectal adenocarcinoma treated at our tertiary care center. These case reports expand the current knowledge base and provide valuable insights into managing this rare condition.

PATIENT DESCRIPTION

CASE 1

A 22-year-old healthy male with no family history of neoplasm was referred to our hospital after undergoing a colonoscopy at an outpatient facility due to recurrent rectal bleeding. The colonoscopy revealed 20 large, pedunculated polyps up to 15 mm in the right colon and 10 additional smaller polyps in the rectum. The endoscopic appearance was described as hamartomatous. He was initially diagnosed with an oligopolyposis disease of unknown cause, necessitating further investigation, including a repeat colonoscopy and an eye examination for congenital hypertrophy of the retinal pigment epithelium to determine familial adenomatous polyposis, and genetic testing for mutations linked to hamartomas and familial polyposis.

A follow-up colonoscopy revealed 20–30 large, pedunculated polyps throughout the large intestine. Pathology from these polyps confirmed hamartomas. In the rectum, an additional large polyp (5 cm from the anal verge) was observed, which was ulcerated, reddish in color, and indurated. Pathology of this polyp showed signet cell adenocarcinoma. Immunostaining for MLH1, MSH2, MSH6, and PMS2 showed intact nuclear expression. Tumor markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were not elevated. A computed tomography (CT) scan of the abdomen and chest showed no signs of distant metastasis to the liver or lungs. A pelvic magnetic resonance imaging (MRI) revealed enlarged mesorectal lymph nodes, suggesting potential lymphatic involvement.

A ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography (^{18}F-FDG PET/CT) demonstrated FDG uptake in the low rectum, consistent with the primary tumor, enlarged mesorectal lymph nodes, and two additional FDG-avid lesions in the large intestine thought to be advanced polyps. The case was discussed at a multidisciplinary tumor (MDT) board meeting. Tumor staging was low-laying T3N2 rectal adenocarcinoma, and the decision was to proceed with total neoadjuvant therapy (TNT). Neoadjuvant therapy consisted of eight courses of mFOLFOX6, followed by capecitabine and rectal radiation. A ^{18}F-FDG PET/CT scan after chemotherapy revealed a marked decline in FDG signals in the rectum. After completing chemoradiation therapy, surgical treatment was indicated. Anoscopy before surgery revealed a 4 cm mass from the anal verge in the left rectal wall with involvement of the anterior part of the sphincter complex.

Due to the location of the mass and findings on the pelvic MRI, total proctocolectomy with end ileostomy was performed 3 months after the completion of chemoradiation therapy. The patient had an uneventful postoperative course. Pathology from the surgery revealed hamartomatous polyps throughout the large intestine, with the rectal lesion showing a complete pathological response and no viable tumor cells. In addition, 44 lymph nodes were examined, none of which showed metastases. A ^{18}F-FDG PET/CT conducted 3 months after surgery indicated no evidence of disease, and the patient continues active surveillance.

CASE 2

A 31-year-old female with no family history of CRC was diagnosed with JPS at the age of 6 years during an investigation for anemia. The patient was hospitalized in our surgical department due to rectal bleeding accompanied by severe fatigue and pallor. A gastroscopy and colonoscopy were performed. The gastroscopy was normal, while the colonoscopy revealed diffuse polyposis disease in the large intestine. The polyps were a mix of pedunculated and sessile, consistent with her known diagnosis of JPS. A large, circular, ulcerated polyp was found in the middle rectum with a high suspicion of malignancy. Pathology from the large colon polyps showed non-neoplastic juvenile-type polyps and neoplastic polyps with juvenile architecture with low-grade dysplasia. Pathology from the rectal polyp confirmed adenocarcinoma. Examination under anesthesia revealed a large circumferential polypoid lesion at the anterior wall of the rectum, 5-6 cm from the anal verge. Tumor markers were not elevated (CEA 1.5 ng/ml, CA 19-9 11.3 U/Ml). A chest CT showed no signs of metastasis to the lungs. An abdominal CT revealed a rectal mass in the mid-upper rectum with irregular margins and no clear plane of separation from the uterus, along with an enlarged lymph node in the mesorectal fat. A pelvic MRI demonstrated a mass located 5 cm from the anal verge, with invasion through the rectal wall into the mesorectal fat at a depth of 1.6 cm. ^{18}F-FDG PET/CT showed a pathological signal in the rectal mass accompanied by perirectal fat stranding. Given the background and the significant genotype-phenotype relationship in JPS, in addition to the young age of presentation with rectal adenocarcinoma, we proceeded with next-generation sequencing, which revealed several known mutations related to JPS: GNAS, SMAD4, ATM, and CYP2D6. The case was presented at the MDT board meeting. A treatment plan was developed to proceed with TNT for the patient's diagnosis of mid-rectum cT3N0M0 adenocarcinoma.

After completing neoadjuvant therapy, the MDT board reconvened to review the latest ^{18}F-FDG PET/CT scan, which demonstrated significant regression of the mid-rectal tumor. However, it also revealed extensive signals throughout the large intestine, indicating a high polyp burden. Given the substantial number of polyps and the residual positive signals in the mid-rectum, the decision was made to proceed with a total proctocolectomy and end ileostomy. The patient underwent the surgery without any intraoperative or postoperative complications and was discharged home on postoperative day 9. Pathology from the surgery showed complete pathological response. The patient continues active surveillance in the outpatient clinic to date.

COMMENT

These two cases highlight the complexities of treating JPS patients with rectal cancer. Key considerations when determining suitable surgical treatment include the age of presentation, polyp burden, the extent of the resection, the risk of CRC recurrence, and the potential negative impact on the patient's quality of life. On diagnosing colorectal cancer in patients with JPS, the surgical options range from segmental colonic resection to proctocolectomy with ileal pouch-anal anastomosis (IPAA), proctocolectomy with end ileostomy, or proctocolectomy with continent ileostomy. Segmental colonic resection, if feasible for achieving negative pathological margins, can preserve intestinal continuity and minimize the impact on quality of life. However, this approach carries the risk of recurrence and necessitates lifelong endoscopic surveillance [5]. Alternatively, total

proctocolectomy with IPAA can omit the need for colonoscopic screening and reduce the risk of colorectal cancer recurrence; however, it is associated with the potential short- and long-term complications such as leakage from the IPAA, pelvic sepsis, pouchitis, and low anterior resection syndrome. Continent ileostomy may be considered for patients with failed IPAA, challenging pelvic anatomy, or at high risk for rectal cancer due to aggressive mutational genotypes, such as SMAD4.

A better understanding of the genotype-phenotype interplay is needed to provide an individualized and tailored approach. Although the focus is often on resection once cancer is diagnosed and endoscopic surveillance is generally considered safe, the psychosocial and economic costs of lifelong surveillance are not fully understood

CONCLUSIONS

The treatment plan for patients with JPS and rectal cancer should be tailored to each patient. This planning requires selecting the most appropriate surgical option in collaboration with the patient, considering their ability to adhere to lifelong surveillance, the impact on their quality of life, and the risk of rectal cancer recurrence. Careful and comprehensive decision making by a multidisciplinary team is crucial in formulating an effective treatment plan for these patients.

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Capsule

Running on myelin

Running a marathon requires an extraordinary amount of energy expenditure, and exercise has been associated with structural brain changes in animal models. **Ramos-Cabrer** and colleagues investigated the short- and long-term effects of running a marathon on brain structure using functional magnetic resonance imaging (fMRI). The authors found a temporary reduction in myelin in regions of the brain associated with motor activity, sensory perception, and emotional responses in subjects after they completed a marathon. Two months after the marathon, myelin levels were fully restored, suggesting that myelin might be used as fuel during long-lasting activities when energy demands are extreme.

Nat Metab 2025; 7 (4): 697
Eitan Israeli

Capsule

Social disadvantage accelerates aging

Social disadvantage, like advanced age, is a risk factor for a broad range of health conditions; however, whether it influences the aging process remains unclear. Using a multicohort approach, **Kivimaki** and colleagues investigated the associations of social disadvantage with age-related plasma proteins and age-related diseases. The authors found proteomic signatures of accelerated immune aging and 14 specific age-related proteins linked to social disadvantage during both early and later life. Individuals experiencing social disadvantage had an increased risk of 66 age-related diseases, with up to 39% of these associations mediated by the 14 age-related proteins (e.g., DNAJB9, F2, HSPA1A, BGN). The main enriched pathway involved the upregulation of the pro-inflammatory regulator NF-κB24 and its downstream factor interleukin-8. These findings support the hypothesis that social disadvantage throughout the life course may accelerate aging, a biological mechanism that could explain why social stratification plays such a fundamental role in determining human health.

Nature Med 2025; 31: 1635
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