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CASE REPORT

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Genetic analysis for diagnosing local recurrence of sigmoid colon cancer mimicking a small intestinal tumor: a case report

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Abstract

Background With recent advances in genetics research, genetic analysis is increasingly being used in clinical practice. We report a case in which genetic analysis aided in diagnosing a local recurrence of sigmoid colon cancer, initially suspected to be a primary neoplasm of the small intestine.

Case presentation A 61-year-old male underwent laparoscopic sigmoidectomy for stage IIIB sigmoid colon cancer, followed by 8 cycles of CAPOX adjuvant chemotherapy, one and a half years prior. A follow-up CT scan performed one and a half years postoperatively revealed a mass in the small intestine near the ileal end, adjacent to the staple line of the previous colonic anastomosis. PET imaging showed high uptake in the small intestine but no significant uptake at the site of the prior anastomotic ring. Based on these findings, a primary small intestine neoplasm was suspected, rather than a local recurrence of the sigmoid cancer, prompting laparoscopic surgery. Intraoperative findings revealed an inflamed mass in the ileum, approximately 30 cm proximal to the cecum, involving staples from the previous anastomotic site. Consequently, an ileocecal resection combined with resection of the prior colonic anastomosis was performed. Macroscopically, the resected specimen revealed a 25-mm Type 2 tumor in the ileum extending into the previous anastomotic site of the large intestine, while the colonic mucosa remained intact. Histopathological examination identified a moderately differentiated tubular adenocarcinoma, consistent with the histology of the primary sigmoid cancer, raising the possibility of local recurrence. To analyze the origin of the ileal tumor, we performed whole-genome sequencing and subsequent PCR direct sequencing. As a result, identical mutations in two key driver genes (*KRAS* c.35G > A and *PIK3CA* c.1624G > A), as well as a mutation in a passenger gene (*BBS9* c.2218_2222del), were identified in the primary and ileal tumors. These findings confirmed that the ileal tumor was a local recurrence rather than a new primary malignancy.

Conclusions The present case highlights the practical application of genetic analysis in clinical practice, particularly when clinical diagnosis and histopathological findings are inconclusive or conflicting.

Keywords Whole-genome sequencing, Genetic analysis, Local recurrence, Invasion to small intestine

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Background

In recent years, advances in genetics research have positioned genetic analysis as a potentially significant tool not only in research but also in clinical practice [1–4]. Since cancer is increasingly recognized as a "disease of the genome," genetic analysis has gained prominence in the field of oncology [5]. Despite its recognized importance, routine implementation of genetic analysis in daily clinical practice remains challenging. Barriers such as high costs, limited access to testing, and a lack of familiarity and acceptance among clinicians and patients hinder broader adoption [1]. Learning from case reports that demonstrate practical applications of genetic analysis can help lower these barriers and encourage its use in clinical decision-making.

Here, we report a case in which genetic analysis facilitated the diagnosis of a local recurrence following sigmoidectomy, initially suspected to be a primary neoplasm of the small intestine. By strategically combining whole-genome sequencing with targeted PCR direct sequencing, this case illustrates how genetic analysis can be effectively integrated into clinical practice to achieve an accurate diagnosis.

Case presentation

A 59-year-old male presented with pain in the lower abdomen and epigastric region. Colonoscopy revealed circumferential stenosis, preventing the scope from passing through the stricture in the sigmoid colon. The preoperative diagnosis was sigmoid cancer, and the patient underwent laparoscopic surgery. Intraoperative findings revealed a mass in the sigmoid colon near the sigmoid-descending junction, with macroscopic invasion of the abdominal wall, necessitating partial resection of the abdominal wall along with the resection of the sigmoid colon. No small bowel loops were in close proximity to the tumor. Laparoscopic sigmoidectomy with partial abdominal wall resection and D3 lymphadenectomy was performed.

The resected specimen showed a circumferential tumor, measuring 40 × 35 mm, with a proximal margin of 10 cm and a distal margin of 14 cm. Pathological assessment revealed moderately differentiated tubular adenocarcinoma with some poorly differentiated components. Based on the Union for International Cancer Control (UICC) TNM classification (8th edition), the tumor was staged as pT4a N1b (2 out of 35 retrieved lymph nodes were positive) M0, corresponding to stage IIIB. The final pathology confirmed T4a disease with no microscopic invasion of the bladder, and the circumferential resection margin was negative, indicating an R0 resection. Genetic mutation analysis showed positivity for KRAS G12D, negativity for BRAF V600E, and microsatellite stability (MSS). The patient received adjuvant chemotherapy with the CAPOX regimen (8 cycles of capecitabine and oxaliplatin).

A follow-up CT scan, performed one and a half years postoperatively, revealed a mass in the small intestine near the ileal end, adjacent to the staple line of the previous colonic anastomosis, with signs of lymphadenopathy (Fig. 1A). Axial PET imaging demonstrated high uptake at the site of wall thickening seen in the small intestine near the "dog-ear" staple line (Fig. 1B and C), but no significant uptake at the site of the prior anastomotic ring (Fig. 1D). Blood tests, including tumor markers (CEA and CA19-9), were unremarkable. Based on these findings, a primary small intestine neoplasm was suspected rather than a local recurrence of the sigmoid cancer, prompting laparoscopic surgery. Intraoperative findings revealed an inflamed mass in the ileum, approximately 30 cm proximal to the cecum (Fig. 2A), involving staples from the previous anastomotic site (Fig. 2B). Consequently, an ileocecal resection with resection of the prior colonic anastomosis was performed.

The resected specimen revealed a 25-mm ulcerated tumor with clear margin in the ileum (Fig. 3A and B), extending into the previous anastomotic site of the large intestine. Macroscopically, the colonic mucosa remained intact without tumor exposure (Fig. 3C). Based on these macroscopic findings, a primary small intestine neoplasm was suspected. Histopathological examination, however, identified a cribriform structure, indicating moderately differentiated tubular adenocarcinoma with some poorly differentiated components, similar to the histological characteristics observed in the initial surgical specimen. The tumor originated from the lamina propria of the large intestine, extended to the subserosa, and was exposed on the mucosal surface of the small intestine (Fig. 4A and B). No lymph node metastasis was observed among the 42 retrieved lymph nodes. These findings raised the possibility of a local recurrence.

To investigate this possibility, we carried out genetic analysis of the three samples including sigmoid cancer (T1) from the tissues obtained in the first operation, and the ileal tumor (T2) and non-cancerous colonic mucosa (N) from the second operation. Whole-genome sequencing of T2 and N samples identified two driver mutations, *KRAS* c.35G > A (p.G12D) and *PIK3CA* c.1624G > A (p.E542K), in T2 with a variant allele frequency of 0.43 and 0.39, respectively. In addition to these two driver mutations, we identified a number of potent passenger mutations including *BBS9* c.2218_2222del (p.L740Afs*4) with a variant allele frequency of 0.35. To examine the presence or absence of these mutations, we performed PCR direct sequencing with the DNA of N, T1, and T2 by Sanger's sequencing (Fig. 5). As depicted in the four-color electrochromatogram (Adenine: green, Thymine: red, Guanine: blue, Cytosine: turquoise), T1 and T2 samples,

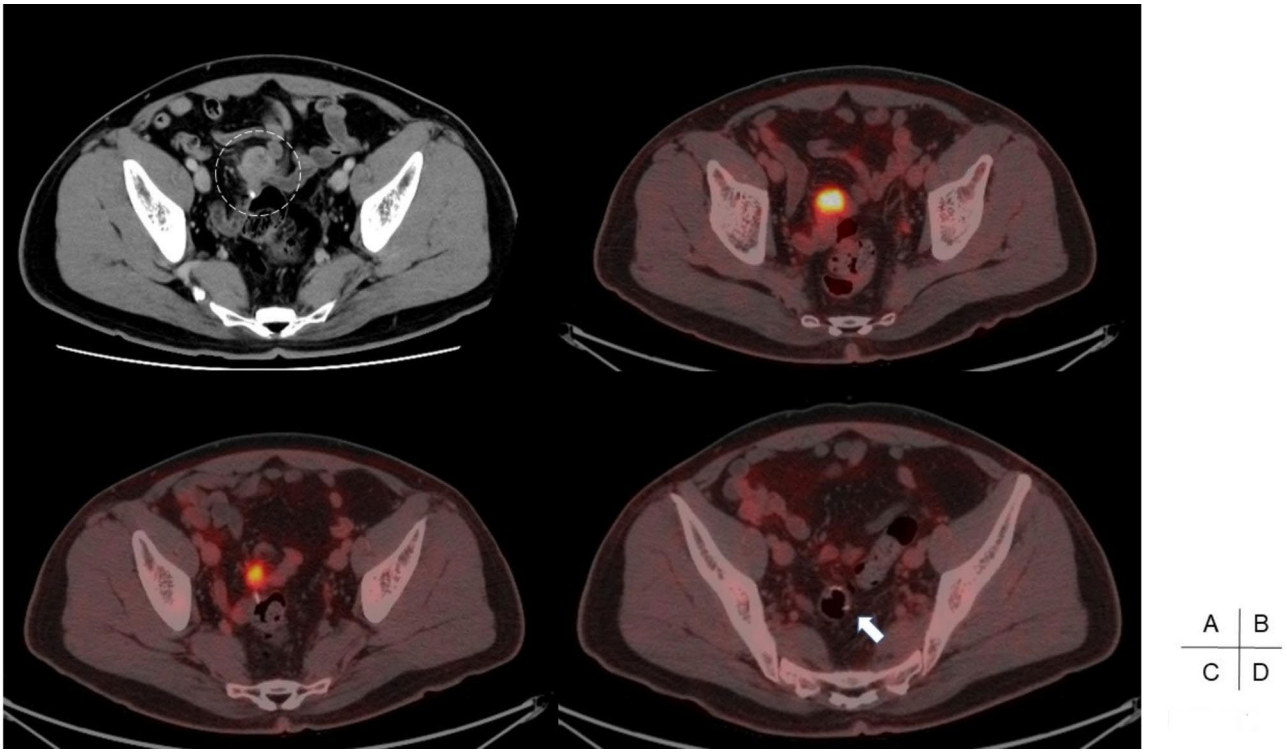

Fig. 1 CT and PET scan findings. (**A**) Axial CT image showing wall thickening of the small intestine (dotted white circle) near the previous anastomotic site. (**B**) Axial PET image showing high uptake at the site of wall thickening seen in (**A**). (**C**) Uptake was seen at the site of the "dog ear" staple line. (**D**) Uptake was not seen at the site of the anastomotic ring (arrow)

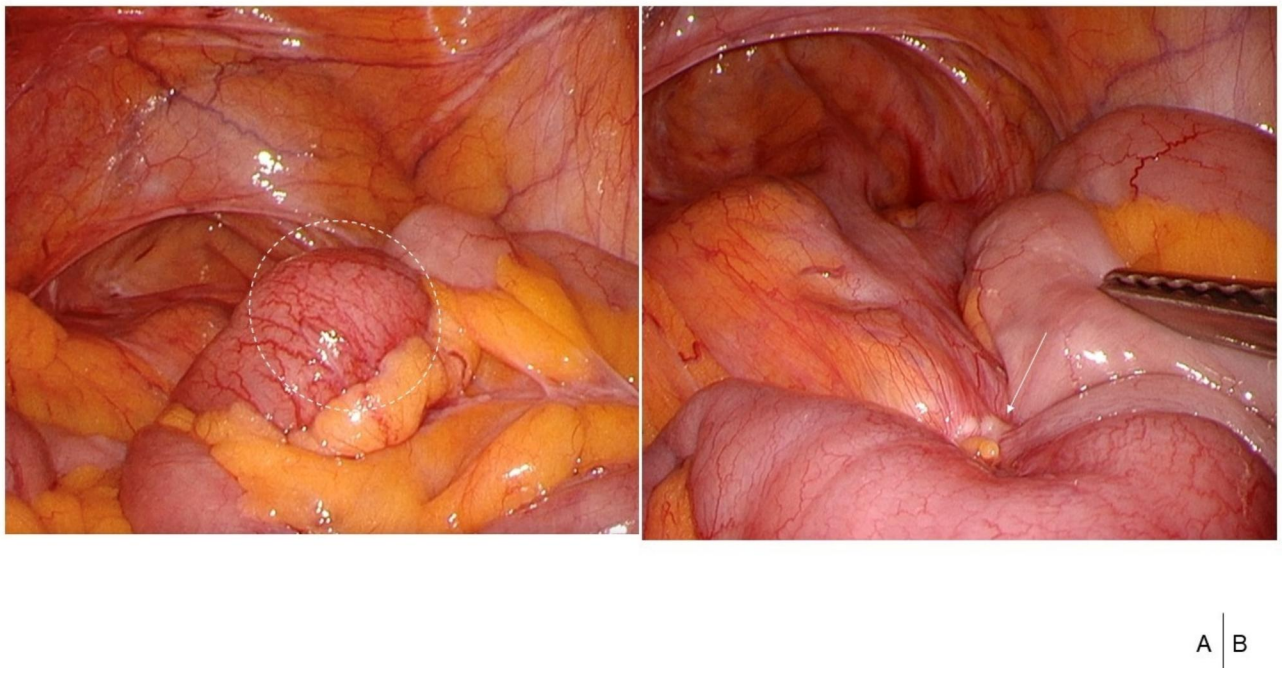

Fig. 2 CT findings. (**A**) Inflamed mass at ileum (the dotted white circle), 30 cm proximal from the cecum. (**B**) The arrow points to the staples from the previous anastomotic site, which was involved by the mass

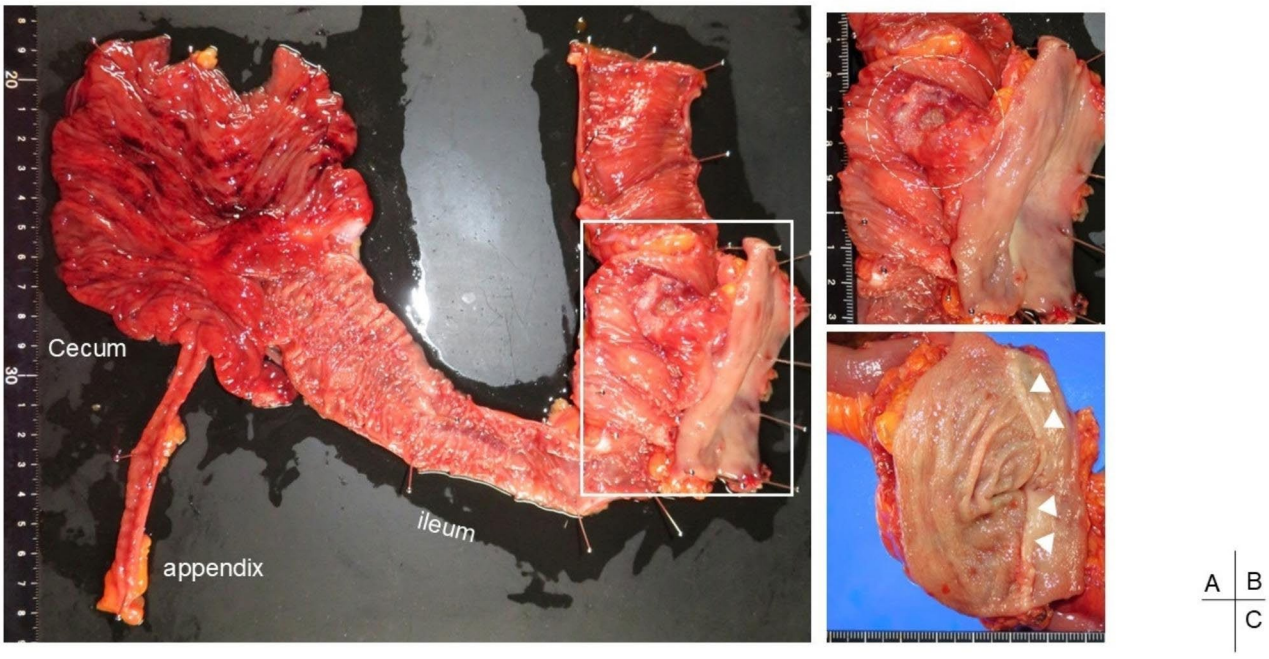

Fig. 3 Surgical specimen. (**A**) Resected specimen from the ileocecal resection with partial resection of the large intestine. (**B**) Magnified image from the white area in (A). The dotted white circle corresponds to a 25 mm Type 2 tumor at the ileum, adjacent to the large intestine. (**C**) Magnified image of the mucous surface of the large intestine. Arrow heads point to the anastomotic line from the previous operation. There was no exposure of the tumor to the mucous surface of the large intestine

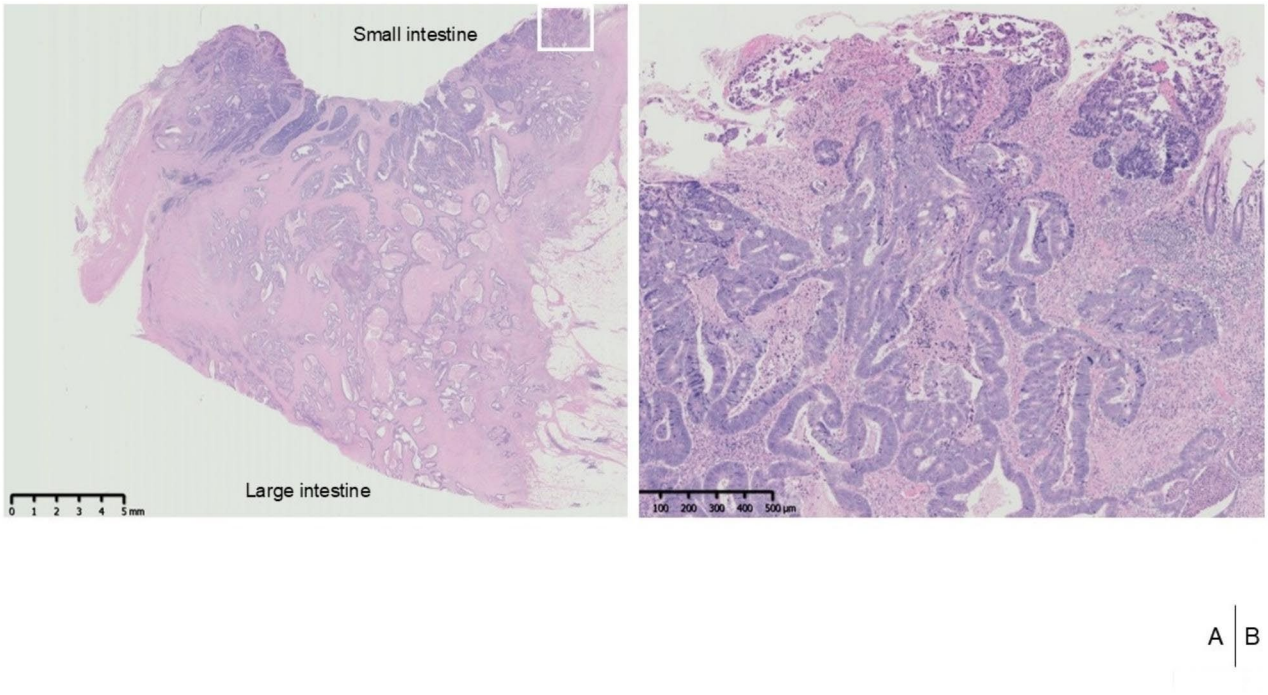

Fig. 4 Histology image of the resected specimen. (**A**) H&E staining of the resected specimen of the ileum. A tumor originating from the lamina propria of the large intestine extended to the subserosa and was exposed at the small intestine's mucosal surface. (**B**) Magnified image of the white square in (**A**) showing a cribriform structure indicating moderately differentiated tubular adenocarcinoma as well as some poorly differentiated tubular adenocarcinoma

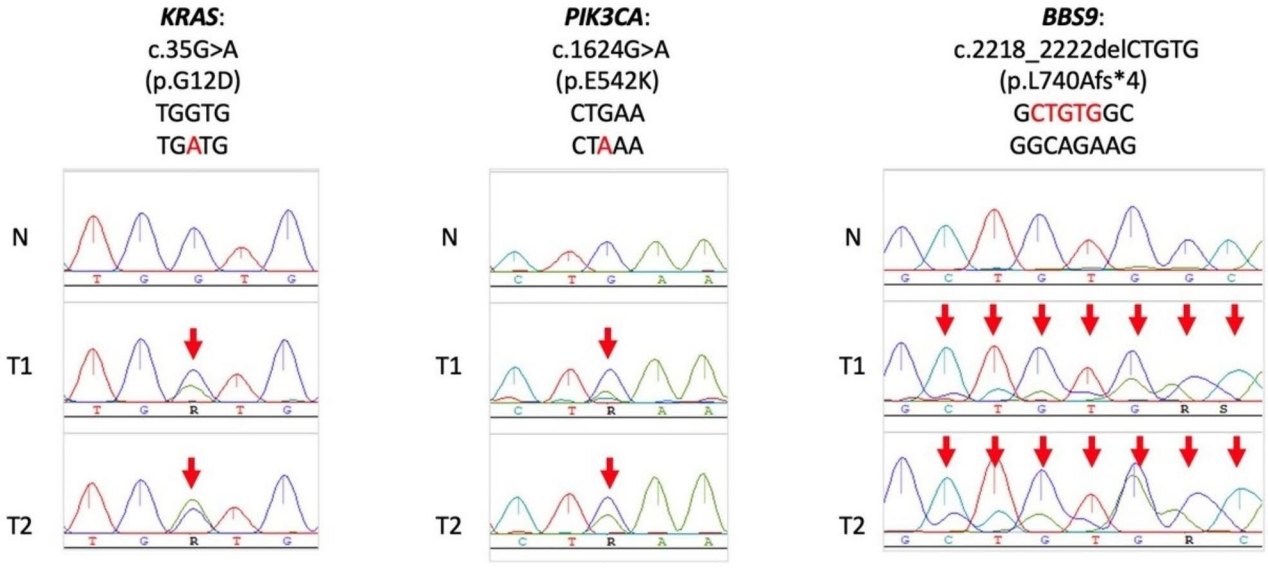

Fig. 5 Results of the genetic analysis. Four-color electrochromatogram of the Sanger's sequencing run of 3 samples: normal colonic mucosa (N), sigmoid colon cancer from the first operation (T1), and resected sample from second operation (T2). Red arrow points out the same pattern of the peak seen at the same nucleotide in T1 and T2, indicating that both samples have the same origin

but not the normal sample (N), shared the same somatic mutations in the three genes, indicating that both tumors originated from the same source. These findings confirmed that the ileal tumor was a local recurrence of the sigmoid colon cancer rather than a new primary malignancy. Consequently, the patient underwent six months of adjuvant chemotherapy.

Postoperative recovery was uneventful, and the patient was discharged after 7 days. As of the one-year follow-up from the second operation, the patient remained free from both local recurrence and distant metastases.

Discussion and conclusions

We encountered a case of advanced sigmoid colon cancer with local recurrence, which mimicked a primary small intestine tumor. This case is noteworthy because all clinical features, including preoperative evaluation, intraoperative findings, and postoperative macroscopic assessment, initially suggested a primary small intestine neoplasm. However, histological examination raised the possibility of local recurrence, and the final diagnosis — local recurrence rather than a primary small intestine neoplasm — was confirmed through genetic analysis. This distinction was crucial, as it led to the initiation of six months of adjuvant chemotherapy. Had the diagnosis been primary small intestinal cancer without lymph node metastasis, adjuvant chemotherapy would not have been administered. This case illustrates the potential role of genetic analysis in everyday clinical practice.

Small intestine neoplasms are rare, accounting for only 0.6% of new cancers and approximately 3% of all gastrointestinal tumors [6, 7]. The incidence of multiple primary cancers is also very low [8]. Therefore, from a statistical perspective, the likelihood of this case being a primary small intestine neoplasm with metachronic double cancer (multiple primary cancers) is extremely low. However, our case initially appeared to be a primary neoplasm of the small intestine. This assumption was based on several factors. First, the CT scan and PET scan showed the lesion in the small intestine, rather than at the anastomotic site of the large intestine. Second, intraoperative findings revealed an inflamed mass in the small intestine. Third, postoperative macroscopic inspection showed a Type 2 lesion on the mucosal surface of the small intestine, but not on that of the large intestine. Given these observations, it seemed reasonable to assume that the tumor originated in the small intestine and invaded the adjacent large intestine, suggesting the possibility of multiple primary cancers at different sites.

On the other hand, local recurrence of sigmoid cancer is not uncommon. D'Souza et al. conducted a systematic review and meta-analysis in 2016, finding a local recurrence rate of 10.5% in sigmoid cancer, which was higher than that for rectal cancer [9]. This statistic further supports our final diagnosis, based on genetic analysis, of local recurrence.

Histological findings supported the diagnosis of local recurrence, despite the tumor being exposed on the mucosal surface of the small intestine rather than that of the large intestine. The specimen from the second operation primarily showed a cribriform structure, characteristic of moderately differentiated adenocarcinoma, with some areas of budding and poorly differentiated components. This differentiation pattern resembled that

seen in the specimen from the first operation. The reason for the tumor's exposure on the mucosal surface of the small intestine, rather than the large intestine, may be explained by the theory that the tumor originated from the lamina propria of the large intestine and extended into the small intestine as a submucosal tumor. Over time, the tumor could have eventually exposed itself on the mucosal surface of the small intestine. However, this theory could not be conclusively proven based solely on the histological findings.

In the present case, genetic analysis was the definitive investigation to determine the origin of the tumor, i.e., whether it was a primary neoplasm of the small intestine or a local recurrence of the sigmoid colon cancer. Instead of performing gene panel sequencing, we opted to perform whole-genome sequencing on the secondary sample (T2) to identify both driver and passenger mutations. These mutations were then cross-referenced with the Catalogue of Somatic Mutation in Cancer (COSMIC) database. Among the passenger mutations in the T2 sample, we selected the mutation *BBS9* c.2218_2222del because the mutation had not been reported or deposited in the COSMIC database. Since the two tumors (T1 and T2) shared the same mutations in the three genes, we conclusively determined that the tumor from the second operation was a local recurrence of the tumor from the first operation. This approach is effective because we can survey somatic single nucleotide variants as well as structural variants including copy number variants in the secondary tumor, which may allow for the selection of therapeutic options, although the cost remains higher than that of gene panel sequencing. In addition, we can apply the mutation data in the postoperative surveillance of disease recurrence by liquid biopsy.

The genetic analysis enabled us to reach a definitive diagnosis, which would have otherwise been difficult. In recent years, genetic analysis has become an increasingly important tool in clinical practice. A similar case, reported by Ikushima et al., involved a patient with a history of cervical squamous cell carcinoma who developed ileal squamous cell carcinoma. Whole-genome sequencing revealed that both tumors were of the same origin due to transdifferentiation [10]. While whole-genome sequencing is still limited to a small number of institutions and remains costly, combining it with PCR direct sequencing, as was done in the present case, could make it more accessible and feasible in everyday clinical practice in the near future.

While the clinical applications of genomic technology continue to expand, its utility extends beyond the detection of tumor recurrence. One notable application is pharmacogenomics, where genetic testing facilitates the identification of patients at risk of adverse drug reactions and enables the personalization of drug therapies to improve efficacy, particularly in antiplatelet therapy [11]. Additionally, genomic testing has proven invaluable in diagnosing previously unidentified diseases, particularly in cases where conventional diagnostic methods are inconclusive. This has been especially beneficial in neonatal medicine, where rapid genetic analysis enables early and accurate diagnoses [12]. Furthermore, genetic testing plays a crucial role in risk assessment and preventive medicine. By identifying individuals with hereditary cancer predispositions, clinicians can implement tailored management strategies, including prophylactic surgeries to reduce cancer risk [13]. These examples underscore the expanding role of genomic medicine and its growing impact on clinical practice.

In summary, we encountered a case in which the tumor's origin was unclear until genetic analysis was performed. This underscores the importance of considering genetic analysis in clinical practice, as it can provide clarity in diagnosing conditions that may not be conclusively determined through other investigations.

Abbreviations

COSMIC	Catalogue of somatic mutation in cancer
MSS	Microsatellite stable
UICC	Union for international cancer control

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Author contributions

GI designed the report, analyzed the data, and prepared the draft of the manuscript. YF and KY collected and analyzed the genetic data. SM and YA collected the patient's clinical data. YO collected pathological images. DS designed the report and was responsible for writing the manuscript. All authors coordinated and helped draft the manuscript, and read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

In our institute, approval of the ethics committee for the retrospective analysis of a clinical case report is not required.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Competing interests

The authors declare no competing interests.

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