CASE REPORT

Patient with Lynch syndrome with subsequent development of small bowel adenocarcinoma

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Accepted 20 May 2018

SUMMARY

Small bowel adenocarcinoma (SBA) is a rare cancer in the general population, but the incidence increases in patients with Lynch syndrome. The present case describes a 57-year-old white woman with a history of colon cancer status posthemicolectomy and diagnosis of Lynch syndrome. Twenty years after her operation, the patient presented with vague abdominal discomfort and constipation, and underwent an exploratory laparotomy which revealed a stage 3A SBA. Genetic testing of the specimen provided evidence of microsatellite instability and faulty DNA repair supporting aetiology of Lynch syndrome. This case is unique in that SBA, if present in patients with Lynch syndrome, is usually a presenting symptom and has not been widely described in literature as an occurrence so many years after. As a result, this case highlights the importance of a low threshold for a thorough evaluation in patients with Lynch syndrome who present with signs of small bowel obstruction.

(NCCN) for individuals with Lynch syndrome, which include colonoscopy every 1–2 years starting at the age of 20–25 years and annual transvaginal ultrasound and endometrial sampling of the uterus for colorectal and endometrial cancers, respectively, there are no current routine surveillance guidelines for the less frequently associated neoplasms, such as SBA.⁶ This means that SBAs in these patients are detected later and in more advanced stages. Moreover, the presenting symptoms of SBA are non-specific, further postponing diagnosis.³ The following case describes a female patient, with delayed diagnosis of Lynch syndrome, who presents with an incidental finding of SBA during exploratory laparotomy for lysis of small bowel adhesions 20 years after resection of metastatic colon cancer. This case highlights the importance of having a high clinical suspicion for SBA in patients with Lynch syndrome, who present with small bowel obstruction symptoms and anaemia.

BACKGROUND

Small bowel carcinoma is a rare neoplasm, accounting for less than 5% of gastrointestinal (GI) cancers and 0.5% of all cancers in the USA.^{1,2} While four histological types of small bowel cancer exist, adenocarcinoma accounts for roughly 40% of these neoplasms, making it the most common along with carcinoid tumours. While small bowel adenocarcinoma (SBA) can occur in any part of the small intestine, the duodenum is the most frequently involved location, accounting for roughly 55% of SBAs.³ Although there is an increasing incidence of SBA, with an estimate of 5300 new cases in the USA per year,¹ pathogenesis and aetiological factors remain limited due to its rarity. Nonetheless, 5%–35% of SBA cases were found to have inactivating mutations in the DNA mismatch repair (MMR) genes (MLH1, MLH2, MSH6) commonly seen in Lynch syndrome, previously known as hereditary non-polyposis colorectal cancer, giving rise to a potential common carcinogenesis pathway between a certain type of colon cancer and SBA.^{1,3}

Lynch syndrome, the most common cause of hereditary colon cancer, is an autosomal dominant condition that predisposes adults to a variety of other neoplasms, mainly uterine (endometrial), ovarian and gastric carcinomas. Yet, there exists a susceptibility to less common cancers, including cancer of the small bowel with a lifetime risk of 1%–4%.^{4,5} Despite screening recommendations from the National Comprehensive Cancer Network

CASE PRESENTATION

A 57-year-old woman with a history of metastatic colon cancer isolated to the left lateral liver and 3 out of 12 colonic regional lymph nodes, status posthemicolectomy, partial liver resection, and adjuvant chemotherapy with 5-fluorouracil (5-FU) and leucovorin at the age of 36, presented to the hospital with diffuse abdominal pain and constipation for over 2 months, concerning for a small bowel obstruction. Family history is pertinent for multiple relatives with colon cancer in their 30s, with the most recent relative being her daughter, who was diagnosed with colon cancer in her late 30s and subsequently passed away at the age of 39. The daughter, who screened positive for Lynch syndrome at the time of her colon cancer diagnosis, subsequently underwent confirmatory genetic testing and was found to be positive for Lynch syndrome. Based on her daughter's results, the patient also underwent testing for specific Lynch syndrome germline mutations in 2013 and was found to carry a pathogenic mutation in the MLH1 gene: MLH1 p.R100X (c.298C>T), confirming her diagnosis of Lynch syndrome. Surgical history is significant for right and transverse hemicolectomy with enterocolonic anastomosis along with partial liver resection 20 years prior to current presentation, and a total abdominal hysterectomy with bilateral salpingo-oophorectomy for abnormal uterine bleeding unrelated to malignancy.

Physical examination revealed mild and diffuse abdominal tenderness with no rebound or rigidity.

To cite: Azizi AH, Inam ZS, Farrell TJ. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2018-225003

Bowel sounds were decreased. The rest of the exam was unremarkable.

INVESTIGATIONS

CT without contrast of the abdomen showed small bowel dilation initiating at the duodenojejunal junction and terminating at the site of previous right hemicolectomy enterocolonic anastomosis, consistent with small bowel obstruction likely secondary to intra-abdominal adhesions. The site of anastomosis was patent. Interestingly, the scan did not show any identifiable masses in the small intestine.

TREATMENT

The patient's symptoms persisted despite medical therapy; a gastrografin enema was subsequently attempted but was ineffective, thus a decision to perform an exploratory laparotomy for possible lysis of adhesions was made. In the operating room, the area of small bowel obstruction was found to be secondary to a poorly defined, centrally ulcerated and circumferentially indurated intraluminal mass measuring 3.0×1.5 cm at the junction of the duodenum and jejunum. The bowel proximal to the mass was dilated, while that distal to the mass was decompressed; there were marked adhesions to the surrounding bowel. Ultimately, an $11 \times 9.0 \times 4.0$ cm specimen of the small bowel distal to the duodenum was resected, allowing approximately a 10 cm margin both distal and proximal to the lesion. A primary anastomosis was performed after resection of the involved small bowel.

OUTCOME AND FOLLOW-UP

Pathology of the resected small bowel demonstrated well-differentiated, invasive adenocarcinoma in the distal duodenum and proximal jejunum of the small intestine. Pathologic staging of the specimen was T4N1M0 according to the tumour-node-metastasis classification of the American Joint Committee on Cancer, giving it a stage IIIA based on its most recent eighth edition.¹⁷ The tumour invaded through the small bowel wall into the muscularis propria of the loop of another portion of small bowel. A single lymph node found in the specimen was positive for metastatic carcinoma. Immunohistochemical testing of the tumour specimen for deficient MMR proteins revealed a loss of expression for both MLH1 and PMS2 gene products, indicating evidence of microsatellite instability (MSI) and faulty DNA repair (table 1). Additional testing via castPCR of the patient's tissue specimen did not detect the presence of BRAF V600E, KRAS or NRAS mutations.

After resection, the patient's abdominal symptoms improved. Adjuvant chemotherapy with either 5-FU/leucovorin alone or with oxaliplatin was discussed during her subsequent oncology visits; ultimately, the decision not to undergo chemotherapy was made. Surgical follow-up 1 month posthospitalisation was significant for pain at the suture sites and iron deficiency anaemia, where she was started on iron supplementation. Follow-up imaging staging with CT of the chest, abdomen and pelvis with

contrast 6 months later provided no evidence of neoplastic disease. Additional patient surveillance included yearly colonoscopy, esophagogastroduodenoscopy and mammography.

DISCUSSION

Cancers of the small bowel, relatively rare malignancies, have an annual incidence rate of 10 190 new cases and 1390 patient deaths per year in the USA.² Among the four histological types of small bowel carcinomas, adenocarcinoma, carcinoid, sarcoma (GI stromal tumours) and lymphoma, SBA has a well-established relationship with some predisposing genetic conditions, one of which is Lynch syndrome.¹³ Although small bowel tumours are often sporadic, there is a >100-fold increased relative risk for developing SBA in Lynch syndrome.^{5 6} While the most common malignancy associated with Lynch syndrome is colorectal carcinoma (CRC), making it the most common inherited colon cancer syndrome, approximately 50% of patients with Lynch syndrome have the small intestine as the first site of malignancy.^{4 8} Furthermore, SBA in Lynch syndrome is found to present at a younger age, roughly 10–20 years earlier, when compared with the mean age of 65 in the general population.^{1 4 5} In this case, our 57-year-old patient presented with SBA 20 years after a diagnosis and consequent resection of colon cancer, delineating that the small intestine does not have to be the first presenting site of malignancy in patients with Lynch syndrome.^{4 8}

The clinical presentation of SBA depends on the location of the tumour and its growth pattern. Symptoms are generally vague and can range from abdominal pain, nausea, vomiting, anaemia, to obstruction.³ Although SBA is an uncommon cause of small bowel obstructions, with adhesions and hernias being the most common, it is observed in jejunal and ileal tumours and, less frequently, in duodenal adenocarcinomas (47% vs 34%, respectively).¹ This lack in specific SBA presenting symptoms as well as the deficiency in effective tools for exploring the small intestine has led to a relative delay in diagnosis, approximately 6–8 months,³ and during more advanced stages, T3 and T4.^{1 4 9} SBA generally has a poor prognosis at all its stages, with a 5-year mean survival rate ranging from 50% to 60% for stage I, 39%–55% for stage II, 10%–40% for stage III and 3%–5% for stage IV,¹⁰ making SBA's prognosis intermediate between that of colon and gastric cancers.^{9 10} Lymph node metastasis and distal small intestine location (jejunum and ileum) have been found to be the most important independent factors determining prognosis,⁹ with nodal metastasis being the main prognostic factor.¹⁰ While current SBA surgery guidelines require the removal of 8–10 regional lymph nodes to investigate for metastasis, as it correlates with improved prognosis,¹¹ only a single lymph node was harvested from our patient's excised tumour; considering that the exploratory laparotomy was performed urgently for small bowel obstruction (SBO)—with significant time spent on lysis of adhesions—rather than with the intention of a tumour resection or a suspicion for SBA, the recommended number of nodes was not removed. Nonetheless, improved 10-year survival is found in the well-differentiated and moderately differentiated compared with that of the undifferentiated subtype (43% vs 0%, respectively).³ Moreover, SBA in Lynch syndrome, although poorly characterised, has been shown to have better long-term survival rates than SBA in the general population.⁶ Although duodenal tumours are less likely to present with more advanced disease than those in other locations in the small intestine, they are linked to a worse overall prognosis.³ This case highlights the need to have a low threshold of suspicion for SBA in patients with delayed diagnosis of Lynch syndrome, who present

Table 1 Summary of patient's immunohistochemical testing results for DNA mismatch repair genes

Marker/tissue	Adenocarcinoma	Normal tissue
MLH1	Negative	Positive
PMS2	Negative	Positive
MSH6	Positive	Positive
MSH6	Positive	Positive

with small bowel obstructive symptoms, especially years after a diagnosis of colon cancer. Moreover, although the patient's pathology revealed well-differentiated adenocarcinoma, she still exhibited a stage IIIA cancer, further supporting the advanced stage due to delayed diagnosis.

Lynch syndrome, an autosomal dominant disorder, has been associated with germline mutations in at least one of the MMR genes (MLH1, MSH2, MSH6 and PMS2); such a defect leads to an increased risk of DNA replication errors, which results in MSI tumours^{5 12}; one such tumour MMR gene mutations predispose to is SBA.¹⁰ Most studies have determined the role of MMR genes in patients with CRC, and it has been reported that MSI is detected in 90% of cancers from patients with Lynch syndrome, which accounts for 1%–2% of overall CRC.¹³ Although MSI is sensitive for Lynch syndrome cancers, it is not specific, as 15%–20% of sporadic colon cancers have MSI.^{12 13} Loss of protein expression for any of the MMR proteins indicates a genetic defect, but it does not differentiate among germline, somatic or epigenetic sources.¹² Approximately 15% of sporadic MSI CRC is found to be caused by acquired somatic CpG methylation of the MLH1 gene promotor rather than germline mutations in the aforementioned MMR genes, as seen in Lynch syndrome.^{10 12 13} Nonetheless, three-fourths of MSI CRC due to epigenetic MLH1 promotor hypermethylation has an acquired BRAF V600E mutation, which is rarely seen in patients with germline-based MMR mutations, indicating BRAF's role in determining sporadic colon cancers.^{13–16} Similarly, BRAF mutations have a role in SBA, as they are infrequent in tumours with germline MMR mutations.¹⁰ Our patient's SBA specimen tested negative for the presence of the BRAF V600E mutation, supporting the finding that her MSI SBA was germline based and further confirming her diagnosis of Lynch syndrome.

While the MSI phenotype can be detected through PCR biomolecular test, lack of MMR proteins' expression can be identified using immunohistochemical methods, and no discordance between the two methods currently exists.¹⁰ Based on the association of the defective MMR (dMMR) genes and colon cancer in patients with Lynch syndrome, the National Institute for Health and Care Excellence in 2017 confirmed a universal screening approach for patients with newly diagnosed CRC to undergo either MSI DNA-based testing or immunohistochemistry analysis of their tumours to guide further follow-up testing for Lynch syndrome.^{12 13} Early identification of Lynch syndrome may reduce further cancer risk through intensive screening, follow-up programmes or prophylactic surgery.¹² Recent guidelines from the American Society of Clinical Oncology recommend dMMR screening in patients with CRC, as establishing a diagnosis of Lynch syndrome and subsequent active management of cancer risk has been demonstrated to benefit gene mutation carriers; even more so, the diagnosis creates prevention opportunities in all at-risk relatives.¹³ Although our patient was diagnosed with colon cancer 20 years prior to her presentation with SBA, she underwent genetic testing via direct germline testing for MMR genes at the time of her daughter's CRC diagnosis. Her daughter was screened for Lynch syndrome based on the revised Bethesda Guidelines via immunohistochemical analysis of her CRC and subsequent confirmatory germline testing for MSH2/MLH1.¹² Our patient's positive molecular evaluation supports the previous statement that establishing a diagnosis of Lynch syndrome can confer prevention opportunities in at-risk relatives—in this case, the patient, as she was genetically counselled on her Lynch syndrome test results, provided with current cancer screening guidelines, and given information on testing strategies for her four other living children.

The characterisation of biological factors and information regarding somatic genetic alterations that occur in SBA carcinogenesis have previously been lacking; the limitation in such information can be attributed to the low number of SBA tumours collected secondary to the disease's low incidence.^{9 10 17} Moreover, chemotherapy agents used in patients with advanced stage SBAs (fluoropyrimidines, platinum and irinotecan) are generally the same as those used to treat patients with advanced CRC⁹; yet, similarly, limited data exist on the role of biological factors in targeted therapy for patients with SBA, although adjuvant chemotherapy may improve prognosis and outcome in cases of invaded lymph nodes (stage III disease).^{10 11} Despite the latter, our patient did not undergo adjuvant chemotherapy with 5-FU because of the favourable characteristics of her disease (high MSI and well differentiated) along with the full resection of her tumour (negative margins), which made it possible to undergo watchful waiting and close follow-up. Moreover, it was believed by oncology that her previous treatment with 5-FU/leucovorin for her colon cancer did not aid in controlling the disease process, but rather it was the high MSI nature and complete resection of her CRC that did. Nonetheless, recently, few studies have investigated the role of several candidate genes or their protein expression in the genetic pathway of SBA as both prognostic value and role in targeted treatment.^{9 10 17 18} Of the candidate genes investigated in these recent studies, four classes were examined in our patient: MMR, KRAS, BRAF and NRAS.

Aparicio *et al* found that the dMMR phenotype, defined as either high-level tumour DNA MSI or loss of tumour protein expression of MLH1, MSH2, MSH6 or PMS2, was present in 23% of SBAs, of which Lynch syndrome was suspected in 64% of these tumours; the majority of these dMMR tumours were not related to methylation mechanisms in MLH1 but rather to germline mutations.¹⁰ The incidence of SBA in Lynch syndrome appears to be higher in MLH1 and MSH2 carriers.⁵ In agreement with their findings, our patient, who was confirmed to have Lynch syndrome via genomic testing 4 years prior to her current presentation, expressed a dMMR SBA, as she had a loss of protein expression in both MLH1 and PMS2 (table 1). It has been found that a germline pathogenic variant in MLH1 results in loss of expression of both MLH1 and PMS2 proteins, because of the nature of MMR gene products to function as dimers; this variant may be what was seen in our patient.⁵ The study also found that dMMR tumours were observed more frequently in proximal SBAs (duodenum and jejunum) than distal ones (ileum); their finding suggested that proximal tumours were more likely due to Lynch syndrome.¹⁰ Similarly, previous reports have found that SBAs in patients with Lynch syndrome were more frequently found in the duodenum and jejunum.^{1 10} The study also reports that dMMR tumours were associated with better overall survival in univariate analysis, but was statistically insignificant in multivariate analysis; their finding may indicate the better prognostic value of dMMR tumours.¹⁰

While KRAS and BRAF mutations are mutually exclusive in CRC, they have both been associated with resistance and/or lack of efficacy to anti-epidermal growth factor receptor (EGFR) therapy in these large-intestine tumours.^{9 10 14 19} Several studies have been exploring the effects of anti-EGFR agents in SBA; while some case reports have described an effect of these agents as therapy in wild-type KRAS SBA, there is a lack of randomised trials in chemotherapy agents for SBA and thus no standard regimen currently exists.^{9 11} KRAS and BRAF mutations have been little studied in SBA, but similar to CRC, they are mutually exclusive.⁹ Jun *et al* found that KRAS mutations were present in 32% of SBA cases, while BRAF mutations

were rarely encountered and observed in only 1% of a study's tumours; these frequencies are similar to that seen in CRC, indicating that molecular alterations in SBAs are close to those seen in CRC.⁹ As mentioned previously, anti-EGFR therapy has not been evaluated in SBA, but given the findings of similar prevalence of KRAS mutations in SBA and CRC, there may be a potential role as therapy. Jun *et al* suggest that targeted therapies, such as anti-EGFR, could be beneficial in as much as two-thirds of patients with SBA with wild-type KRAS and BRAF genes and metastatic disease.⁹ Despite these similarities between SBA and CRC, a genomic comparison of SBA with CRC and gastric carcinomas found that SBA is a molecularly unique intestinal cancer.^{11 17} Nonetheless, prognostic value of KRAS/BRAF mutations in SBA remains unclear⁹; while Jun *et al* found that patients with KRAS mutations had shorter survival times than those with wild-type genes, the results were not statistically significant. Moreover, it was found that mutation of KRAS was a worse prognostic predictor in SBA of lower pT classification.⁹ In contrast, Aparicio *et al* reported that KRAS mutations were an independent predictor of longer overall survival in patients with stage IV (metastatic) SBA.¹⁰ Thus, larger studies should be done to confirm prognostic value of KRAS and/or BRAF mutations in SBA. Our patient was negative for both KRAS and BRAF mutations; the latter was consistent with the rarity of BRAF mutations in SBA, while the wild-type KRAS may show a tendency for longer survival than those with a mutation.⁹

Analogous to KRAS, mutant NRAS is a potent oncogene that can be found in a wide variety of cancers, including 3%–5% of CRCs and 10%–20% of melanomas^{20 21}; however, activating oncogenic NRAS mutations are rare in SBA, accounting for 1/83 cases.¹⁸ In concordance with the low frequency of NRAS mutations in SBA, our patient's specimen was negative for the mutation.

Many of the cancers that are increased in patients with Lynch syndrome can either be prevented or detected at an early, curable stage with appropriate screening guidelines. However, small bowel tumours do not currently have specific screening recommendations, compared with those of the colon and endometrium, in patients with Lynch syndrome.^{4 5} Nonetheless, analysis of the MMR phenotype, as discussed previously, is recommended in patients with SBA, since it can reveal the presence of Lynch syndrome.^{1 5} There have been considerable advances in endoscopic techniques—such as capsule endoscopy and balloon-assisted enteroscopy, CT, and MRI enterography and enteroclysis in the evaluation of small bowel diseases.^{5 11} Interestingly, further visualisation of the small bowel with CT of the abdomen and pelvis, wireless capsule endoscopy or an upper GI series with small bowel follow-through have been shown to aid in the diagnosis of SBA.^{3 4 11} Abnormalities on CT scan were found in 97% of cases in a study of 35 patients with small bowel tumours, which predicted the presence of cancer in 80% of them. The characteristic finding on CT was a partially obstructing and concentric narrowing in the proximal small bowel, seen with tumours larger than 3 cm.^{3 9 22} Video capsule endoscopy is a first-line tool to detect small bowel abnormalities in non-obstructed patients, and its use has been evaluated in a few cases of Lynch syndrome, but no recommendation as a screening tool has been established.⁵ In the case of our patient, a CT scan performed for small bowel obstructive symptoms indicated abnormalities that warranted an exploratory laparotomy for complete obstruction, which subsequently revealed SBA on both gross and microscopic pathology. Nonetheless, with improved techniques to visualise

Learning points

- ▶ Lynch syndrome predisposes patients to a variety of neoplasms, mainly colon, endometrial and ovarian carcinomas, but there is susceptibility to less common cancers, one of which is small bowel adenocarcinoma (SBA).
- ▶ One should have a high clinical suspicion for an obstructing neoplasm in a patient with Lynch syndrome presenting with signs and symptoms of a small bowel obstruction, especially if imaging cannot exclude a mechanical source and/or the patient has an associated anaemia. Thus, these patients with either small or large bowel obstructions should be worked up more thoroughly than would be otherwise.
- ▶ Although SBAs are rare and are usually the presenting neoplasm in patients with Lynch syndrome, they can appear years later, further enforcing the need to have a lower threshold for these neoplasms in patients with Lynch syndrome, especially if they are symptomatic.
- ▶ Although there are screening recommendations for colon and endometrial cancers in patients with Lynch syndrome, surveillance for small bowel neoplasms remains limited. This means that SBAs are detected later and potentially at more advanced stages, further decreasing its already poor prognosis. Nonetheless, advances in small bowel visualisation may aid in early diagnosis and better outcomes.
- ▶ SBAs can be associated with mutations in DNA mismatch repair (MMR) genes as well as other oncogenes (KRAS). It is important to test these SBA tumours via immunohistochemical or phenotype testing for defective MMR genes and the presence of other genomic mutations (eg, KRAS), as they may indicate an undiagnosed Lynch syndrome or be associated with certain prognostic values and/or resistance to chemotherapy treatment.

the small bowel, earlier detection of SBA and improvement in prognosis may be possible.¹¹

In conclusion, patients with Lynch syndrome have an increased risk for both CRCs and other extracolonic tumours, including small bowel cancers. Mutations in DNA MMR genes are associated with Lynch syndrome and cause an increased susceptibility to malignancies, including SBA. Although screening recommendations from the NCCN for colon and endometrial cancers in individuals with Lynch syndrome exist, the surveillance for small bowel cancers remains limited; nonetheless, advances in small bowel visualisation are emerging and may aid in early detection. Moreover, increases in the understanding of biological factors associated with SBA may uncover their role in prognostication and/or in targeted chemotherapy. This present study describes a case of a female patient with SBA and a delayed diagnosis of Lynch syndrome, who presents 20 years after resection of metastatic colon cancer and 4 years after confirmed Lynch syndrome genomic testing with symptoms of small bowel obstruction. Thus, early screening for cancers of the small bowel should be considered in these high-risk patients, especially with known MMR mutations. More importantly, the threshold for a thorough evaluation of small bowel cancers in patients who subsequently present with vague abdominal symptoms ought to be lower than the general population.

Contributors AHA: acquisition, analysis and interpretation of data; drafting and revising the manuscript critically for important intellectual content. ZSI: analysis and interpretation of data; drafting and revising the manuscript critically for important

intellectual content. TJF: acquisition of data; revising the manuscript critically for important intellectual content. All authors approved the final version of the manuscript to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

- 1 Aparicio T, Zaanani A, Svrcek M, *et al.* Small bowel adenocarcinoma: epidemiology, risk factors, diagnosis and treatment. *Dig Liver Dis* 2014;46:97–104.
- 2 Siegel RL, Miller KD, Jemal A, *et al.* Cancer statistics, 2017. *CA: A Cancer Journal for Clinicians* 2017;67:7–30.
- 3 Kummar S, Ciesielski TE, Fogarasi MC. Management of small bowel adenocarcinoma. *Oncology* 2002;16:1364–9.
- 4 Sun KK, Liu G, Shen X, *et al.* Small bowel adenocarcinoma in Lynch syndrome: A case report. *Oncol Lett* 2016;12:1602–4.
- 5 Shenoy S. Genetic risks and familial associations of small bowel carcinoma. *World J Gastrointest Oncol* 2016;8:509–19.
- 6 Choi YJ, Jung SW, Um JW, Jw U, *et al.* Small bowel carcinoma in young patient detected by double-balloon enteroscopy. *Korean J Gastroenterol* 2011;58:217–20.
- 7 American Joint Committee on Cancer. Small Intestine. *AJCC Cancer Staging Manual*. 8th. New York: Springer, 2017:221–34.
- 8 Jun SY, Lee EJ, Kim MJ, *et al.* Lynch syndrome-related small intestinal adenocarcinomas. *Oncotarget* 2017;8:21483–500.
- 9 Jun SY, Kim M, Jin Gu M, *et al.* Clinicopathologic and prognostic associations of KRAS and BRAF mutations in small intestinal adenocarcinoma. *Mod Pathol* 2016;29:402–15.
- 10 Aparicio T, Svrcek M, Zaanani A, *et al.* Small bowel adenocarcinoma phenotyping, a clinicobiological prognostic study. *Br J Cancer* 2013;109:3057–66.
- 11 de Bree E, Rovers KP, Stamatou D, *et al.* The evolving management of small bowel adenocarcinoma. *Acta Oncol* 2018:1–11.
- 12 Tognetto A, Michelazzo MB, Calabró GE, *et al.* A systematic review on the existing screening pathways for lynch syndrome identification. *Front Public Health* 2017;5:1–7.
- 13 Sepulveda AR, Hamilton SR, Allegra CJ, *et al.* Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline From the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology. *Arch Pathol Lab Med* 2017;141:625–57.
- 14 Bellizzi AM, Frankel WL. Colorectal cancer due to deficiency in DNA mismatch repair function: a review. *Adv Anat Pathol* 2009;16:405–17.
- 15 Loughrey MB, Waring PM, Tan A, *et al.* Incorporation of somatic BRAF mutation testing into an algorithm for the investigation of hereditary non-polyposis colorectal cancer. *Fam Cancer* 2007;6:301–10.
- 16 Sharma SG, Gulley ML. BRAF mutation testing in colorectal cancer. *Arch Pathol Lab Med* 2010;134:1225–8.
- 17 Schrock AB, Devoe CE, McWilliams R, *et al.* Genomic profiling of small-bowel adenocarcinoma. *JAMA Oncol* 2017;3:1546–53.
- 18 Laforest A, Aparicio T, Zaanani A, *et al.* ERBB2 gene as a potential therapeutic target in small bowel adenocarcinoma. *Eur J Cancer* 2014;50:1740–6.
- 19 Sartore-Bianchi A, Moroni M, Veronese S, *et al.* Epidermal growth factor receptor gene copy number and clinical outcome of metastatic colorectal cancer treated with panitumumab. *J Clin Oncol* 2007;25:3238–45.
- 20 Lièvre A, Bachet JB, Le Corre D, *et al.* KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. *Cancer Res* 2006;66:3992–5.
- 21 Irahara N, Baba Y, Nosho K, *et al.* NRAS mutations are rare in colorectal cancer. *Diagn Mol Pathol* 2010;19:157–63.
- 22 Laurent F, Raynaud M, Biset JM, *et al.* Diagnosis and categorization of small bowel neoplasms: role of computed tomography. *Gastrointest Radiol* 1991;16:115–9.

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