

Bicentric lesion of colon cancer with postoperative fever: A case report

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Abstract. Colon adenocarcinoma (COAD) is a malignant tumor type. Fever is the most common postoperative complication of COAD. The present study described the treatment of a patient with early-stage COAD with precancerous colon polyps and the possible cause of postoperative fever. The patient was a 48-year-old woman with intermittent hematochezia, defectation urgency and liquid feces. The patient received surgical treatment, a whole segment from the intestine was removed, which contained a 4-cm-long mass and a 2-cm-long firm mass. Within 3 days after the operation, the patient's

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Abbreviations: CC, colon cancer; CEA, carcinoembryonic antigen; COAD, colon adenocarcinoma; CRP, C-reactive protein; CT, computed tomography; DAB diaminobenzidine; EDTA, ethylene diamine tetraacetic acid; HE, hematoxylin-eosin; HGB, hemoglobin; IHC, immunohistochemistry; RBC, red blood cell; WBC, white blood cell; KRAS, KRAS proto-oncogene, GTPase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α; GNAS, GNAS complex locus; APC, APC regulator of WNT signaling pathway; TP53, tumor protein 53

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Key words: bicentric lesion, colon adenocarcinoma, precancerous colon polyps, postoperative fever

incision healed well, but the body temperature increased to a range of 37.8-38.6°C. The suture was removed on the 10th postoperative day. After another three days, it was discovered that the upper end of the patient's surgical incision split to the anterior rectus abdominis sheath. The patient was provided with recombinant human acidic fibroblast growth factor to promote wound healing. The patient was finally diagnosed with rectosigmoid junction adenocarcinoma and precancerous colon polyps according to pathological examination results. The patient was given intravenous bevacizumab combined with irinotecan hydrochloride and oral capecitabine, and all drugs were repeatedly applied every 3 weeks, and a total of four treatment cycles were used. The cause of this postoperative fever was concluded to be anemia coming from chronic hematochezia and combined with deep wound dehiscence with secondary infection. The present study showcased that low-dose and short-course prophylactic adjuvant therapy is feasible for early-stage COAD with precancerous colon polyps.

Introduction

Colon cancer (CC) is a malignant tumor originating in the colon or rectum with a high case-fatality ratio with more than 600,000 deaths annually (1), and it accounts for $\sim 6.1\%$ of annual tumor incidences worldwide (2-4). Radical surgery is the primary treatment for CC in its early stages (5). Colon adenocarcinoma (COAD) is the most common pathological type of CC (6). Whether to use postoperative chemotherapy and targeted therapy to inhibit tumor recurrence is still ambiguous. Recent research indicated that the EP4 receptor was a promising targeted therapy in CC (7). Furthermore, colon polyps are cell clumps formed on the colon's mucosa and are considered precursor lesions of CC (8,9). The colonic polyps may be categorized as adenomas, hyperplastic polyps and inflammatory polyps (10). Adenomas appear to be the most common type of colon polyp to develop into COAD (10), and surgical resection is the main treatment method for early-stage COAD (11). However, the concurrence of early-stage COAD

and precancerous colon polyps is infrequent and the optimal treatment method for such cases is still controversial. The present study reported a rare case who had a bicentric lesion of early-stage COAD and precancerous colon polyps and presented with a postoperative fever along with anemia combined with deep-wound dehiscence. Blood tests and pathological examinations of the patient were performed at the laboratory of the present hospital, and a whole-genome sequencing of the COAD sample was performed. Based on the test results, the patient was treated with low-dose and short-course prophylactic adjuvant therapy and gained a good curative effect. Through this case, we aimed to offer a diagnosis and treatment plan for this type of patient to better guide clinical drug use in the future.

Case report

A 48-year-old woman first presented at the Dongzhimen Hospital of Beijing University of Chinese Medicine (Beijing, China) in October 2022 with complaints of intermittent hematochezia, defecation urgency and liquid feces, but with no distention or abdominal pain. The patient's information on the medication and examination results follow the timeline from admission to discharge as a clinical course shown in Fig. 1A. Colonoscopy detection suggested an irregular cauliflower-like mass in the rectosigmoid junction a range of 15-19 cm from the anal verge occupying 2/5 of the intestinal lumen (Fig. 1B). Abdominal computed tomography (CT) revealed intestinal stenosis at the rectosigmoid junction (Fig. 1C). Pathological examination of mass tissue obtained by colonoscopy revealed highly-to-moderately differentiated adenocarcinoma (Fig. 1E). Before the operative day, laboratory testing showed a hemoglobin (HGB) level of 91 g/l (normal range, 115.0-150.0 g/l) and a carcinoembryonic antigen (CEA) level of 8.42 ng/ml (normal range, 0.0-4.5 ng/ml). The patient was diagnosed with a malignant tumor of the rectosigmoid junction and anemia. On the 4th day after admission, the patient received surgical treatment. Intraoperatively, a tumor-like mass (Mass 2) was found at the junction of the rectosigmoid colon with a length of 4 cm. Furthermore, a 2-cm-long, firm mass (Mass 1) was palpitated 7 cm above Mass 2. Next, a whole segment from the intestine including Mass 1 and Mass 2 was removed, and end-to-end anastomosis as well as anterior sacral drainage were performed. The bowel excision is presented in Fig. 1D. After the operation, the patient was monitored and was provided with oxygen, indwelling intragastric and urinary catheters, central venous catheterization, nutritional support, increased rehydration fluids. Also, we gave the patient the dressing change once every other day. At the same time, according to the whole genome sequencing (WES) results of Mass 2, the patient was given the Aidi Injection (12) [1,000 ml intravenous (IV) drip once a day (qd)], a traditional Chinese patent medicine with the function of the reducing swelling and dispersing, purchased from Guizhou YiBai Pharmaceutical Co., Ltd., and the Kang Ai Injection (13) (60 ml IV drip qd), a traditional Chinese patent medicine with the function of enhancing the body's immune function, purchased from ChangBaiShan Pharmaceutical Co., Ltd. for antineoplastic activity. Amoxicillin clavulanate potassium [0.3 g IV drip three times a day (tid), purchased from North China Pharmaceutical Co., Ltd.] for anti-infection, omeprazole sodium [40 mg IV drop bid twice a day (bid) from Yangzhou Aaosaibo Pharmaceutical Co., Ltd.] for gastric acid suppression and dopamine hydrochloride injection (100 mg IV drop once, purchased from Beijing Double-Crane Pharmaceutical Co., Ltd.) for increasing blood pressure.

Within 3 days after the operation, the patient's body temperature increased continuously to range 37.8-38.6°C. The patient had a fever, felt cold and had general fatigue. Furthermore, on the first postoperative day, the white blood cells (WBC) and C-reactive protein (CRP) both increased [WBC count, 10.5x10⁹/l (normal range, 3.5-9.5x10⁹/l); and CRP, 87.49 mg/l (normal range, 0.0-10.0 mg/l)]. Furthermore, the patient's HGB and red blood cells (RBC) were decreased [HGB, 82 g/l; and RBC, $3.43 \times 10^{12}/l$ (normal range, $3.8-5.1 \times 10^{12}/l$)]. Blood culture tests for anaerobes and aerobes were performed and the results indicated no bacterial growth (Table I). The incision healed well and the patient was given the transfusion therapy for 1 unit of RBCs, which the erythrocyte suspension, filtered from white cell, coming from other healthy person, was injected into the patient to treat anemia. Aspirin-DL-Lysine Injection for reducing fever, amoxicillin clavulanate potassium [0.3 g IV drip tid, purchased from North China Pharmaceutical Co., Ltd.] and Ornidazole and Sodium Chloride Injection [0.5 g IV drip bid, purchased from Sichuan Kelun Pharmaceutical Co., Ltd.] for anti-infection and XueBiJing Injection [50 ml IV drip, only for two days, purchased from Tianjin Hongri Pharmaceutical Co., Ltd.] with the function of dispelling blood stasis and detoxification to reduce fever (14). The next day, the patient's body temperature gradually decreased to normal and the patient's clinical manifestations, such as feeling cold and fatigue, improved obviously (Fig. 1F).

Within 9 days after the operation, the patient complained of mild pain in the left-sided lower leg, and serum D-dimers increased (4,035 μ g/l; normal range, 0.0-300.0 μ g/l) on the ninth postoperative day. The patient was given a hypodermic subcutaneou sinjection of low molecular weight heparin calcium 4,100 IU qd for 5 days. D-dimers of the patient were decreased to 2,346 μ g/l on the 14th postoperative day (Fig. 1F) and the patient's left-sided lower leg pain improved. The suture was removed on the 10th postoperative day. After another three days, it was discovered that the upper end of the patient's surgical incision had split to the anterior rectus abdominis sheath with a depth of incision of ~1.5 cm and a length of ~2.5 cm, and fat liquefaction was present according to the measured length of the swab and visual observation (data not shown). The patient was externally provided with lyophilized recombinant human acidic fibroblast growth factor (application as a spray qd; Shanghai Tengrui Pharmaceutical Co., Ltd.) and dressing change every day to promote wound healing.

For the pathological examination for the colon lesions, after treatment with 10% dimethylbenzene for 24 h, the lesion tissues were mounted and resected to small pieces that were added into a cassette for dehydration and embedding in paraffin. The paraffin-embedded lession tissues were then sectioned at 4- μ m thickness. Next, the samples were stained with hematoxylin-eosin for histopathological assessment. Finally, light microscopy was used to observe the sections. The pathological examination results were as follows: The resected bowel was 17 cm in length and 7 cm in diameter, and two protuberant masses were observed in it. Mass 1 was low-grade



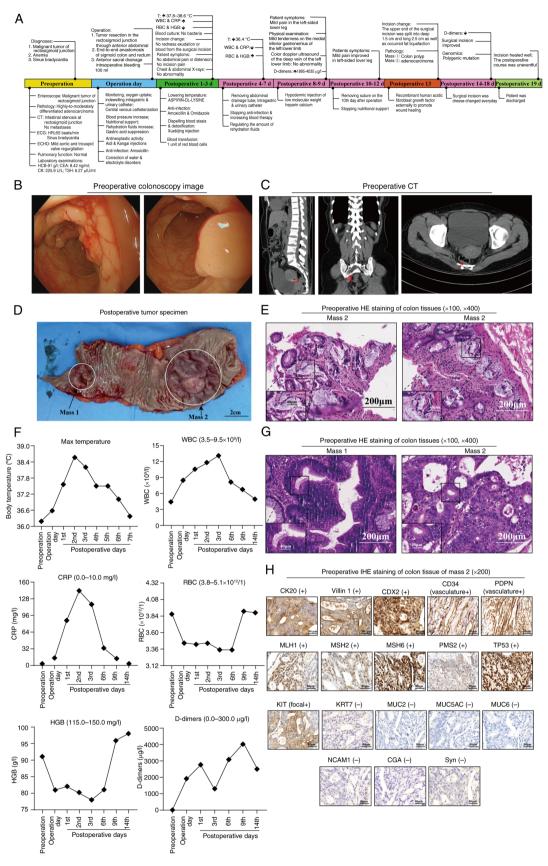


Figure 1. Timeline and examination results for the patient. (A) From the first visit at the hospital to the final discharge, the patient's condition, tests and medication were recorded. (B) Preoperative colonoscopy image. (C) Preoperative abdominal CT scanning images (arrows indicate the tumors). (D) Postoperative tumor specimen (scale bar, 2 cm). (E) Preoperative HE staining of colon tissues (magnification, x100 or x400; scale bar, 200 or 40 μ m). (F) Variation trend of laboratory indicators in the patient, including maximum temperature, WBC, CRP, RBC, HGB and D-dimer. (G) Postoperative HE staining of colon tissues (magnification, x100 or x400; scale bar, 200 or 40 μ m). (H) Postoperative IHC staining of colon tissue of Mass 2 (magnification, x200; scale bar, 80 μ m). IHC, immunohistochemistry; WBC, white blood cells; RBC, red blood cells; HGB, hemoglobin; CRP, C-reactive protein; CT, computed tomography; T, temperature; d, day; HE, hematoxylin and eosin; ECG, electrocardiogram; HR, heart rate; ECHO, echocardiogram; CK, creatine kinase; CEA, carcinoembryonic antigen; TSH, thyroid-stimulating hormone.

Table I. Results of the blood laboratory analysis.

					Time point	ţ			
						Postoperative days	ive days		
Item	Reference range	Preoperation	Operation day	1st	2nd	3rd	6th	9th	14th
WBC, x10 ⁹ /1	3.50-9.50	4.40	8.49	10.50↑	11.70↑	13.10↑	8.20	6.70	5.10
$RBC, x10^{12}/1$	3.80-5.10	3.88	3.45↓	3.43↓	3.45	3.35	3.35↓	3.91	3.89
HGB, g/l	115.00-150.00	91.00↓	81.00↓	82.00	00.08	78.00↓	81.00↓	100.96	00.86
HCT, %	35.00-45.00	28.50↓	25.50	24.90	24.90	24.20	24.60↓	29.40↓	29.80↓
MCV, fl	82.00-100.00	73.40↓	74.10↓	72.80↓	72.10↓	72.30↓	73.60	75.20↓	107.97
MCH, pg	27.00-34.00	23.40↓	23.50↓	23.90	23.20↓	23.40↓	24.10	24.40↓	25.10↓
MCHC, g/l	316.00-354.00	319.00	317.00	328.00	321.00	323.00	327.00	325.00	328.00
RDW-CV, %	10.00-20.00	16.60	15.10	16.60	16.60	16.80	17.10	18.30	21.40 ↑
$PLT, x10^{9}/l$	125.00-350.00	342.00	213.00	213.00	196.00	200.00	233.00	324.00	373.00↑
MPV, fl	6.80-13.50	8.10	9.50	8.90	9.10	09.6	9.70	9.50	9.10
PCT, %	0.11-0.27	0.28 \uparrow	0.20	0.19	0.18	0.19	0.23	$0.31\uparrow$	0.34
PDW, %	9.00-17.00	16.20	15.90	16.70	16.70	16.80	16.70	16.60	16.40
NE, %	50.00-70.00	57.70	89.20↑	91.30↑	\$9.70↓	89.40↑	74.70↑	00.69	60.30
$NE\#, x10^9/1$	1.80-6.70	2.50	7.57↑	09.60	10.50	11.70↑	6.10	4.60	3.10
LY, %	20.00-40.0	31.70	6.70	4.20	4.80	5.10	13.60	19.20↓	29.20
$LY\#, x10^9/1$	0.70-3.80	1.40	0.57	0.40	09.0	0.70	1.10	1.30	1.50
MO, %	0.00-13.00	9.10	3.40	4.20	4.70	4.30	7.50	8.20	00.9
$MO\#, x10^9/1$	0.00-1.20	0.40	0.29	0.40	0.50	09.0	09.0	09.0	0.30
EO, %	0.50-5.00	0.80	09.0	0.20	09.0	09.0	3.70	3.20	3.80
$EO\#, x10^9/1$	0.02-0.50	0000	0.05	0.00	0.10	0.10	0.30	0.20	0.20
BA, %	0.00-2.00	0.70	0.10	0.10	0.20	09.0	0.50	0.40	0.70
$BA\#, x10^9/1$	0.00-0.20	0.00	0.01	0.00	0.00	0.10	0.00	0.00	0.00
CRP, mg/l	0.00-10.00	1.67	13.81↑	87.49↑	143.21	117.21↑	32.90	11.17↑	1.59
Blood culture	Positive	/				Negative	ıtive		
(anaerobic bacteria)									
Blood culture	Positive	/				Negative	ıtive		
(aerobic bacteria)									

hemoglobin concentration; RDW-CV, red cell distribution; CV, coefficient of variation; PLT, platelets; MPV, mean platelet volume; PCT, platelet hematocrit; PDW, platelet distribution width; NE#, number of neutrophils; NE%, percentage of neutrophils; LY%, percentage of abnormal lymphocytes; LY#, number of abnormal lymphocytes; MO%, percentage of monocytes; MO#, number of monocytes; EO%, percentage of eosinophilic granulocytes; EO#, number of eosinophilic granulocytes; BA%, percentage of basophils; BA#, number of basophils; CRP, C-reactive protein; /, not examined; 1, higher than the WBC, white blood cells; RBC, red blood cells; HGB, hemoglobin; HCT, concentration of hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular reference range; ↓, lower than the reference range.



tubulovillous adenoma with focal high-grade intraepithelial neoplasia and Mass 2 was protuberant moderately differentiated adenocarcinoma, invading the shallow muscle layer (Fig. 1G).

Mass 2 was further analyzed by immunohistochemical (IHC) staining. The IHC staining was performed by a third-party company, Servicebio, using an IHC kit (cat. no. PV-9001; Zhongshang Goldenbridge-Bio). Paraffin-embedded colonic mucosa sections were dewaxed and re-hydrated. Antigen retrieval was conducted using EDTA or sodium citrate at 98°C for 20 min. Endogenous peroxidase was blocked with goat serum (Biotopped). Sections were incubated overnight in a humidified chamber with primary antibody to cancer-related genes, followed by biotinylated secondary antibody incubation. Subsequently, diaminobenzidine (DAB) chromogenic reaction was performed using freshly prepared DAB color developing solution. The sections were counterstained with hematoxylin, dehydrated, fixed and mounted. Finally, light microscopy was used to observe the sections with x200 magnification. IHC results were as follows: Tumor-related genes such as cytokeratin 20, Villin 1, caudal type homeobox 2, CD34 (vasculature), podoplanin (vasculature), mutL homolog 1, mutS homolog 2 (MSH2), MSH6, PMS1 homolog 2, mismatch repair system component, tumor protein p53 (TP53) and KIT proto-oncogene, receptor tyrosine kinase (focal) were positive, while keratin 7, mucin 2, oligomeric mucus/gel-forming (MUC2), MUC5AC, MUC6, neural cell adhesion molecule 1, glycoprotein hormones, α polypeptide and synapsin were negative (Fig. 1H). All of the above-mentioned markers were related to promoting the proliferation of colon cancer cells and increase the degree of malignancy of tumors, which further support the pathological diagnosis of COAD.

The results of the WES (performed by the Life Healthcare Group Ltd., CN) of Mass 2 showed that the tumor was of the microsatellite stable type, which is not sensitive to single immunotherapy based on immune checkpoint inhibitors (15). Meanwhile, substitution for aspartic acid to glycine at codon 13 of the KRAS proto-oncogene, GTPase (KRAS-G13D), substitution for alanine to glycine at codon 12 of the KRAS proto-oncogene, GTPase (KRAS-G12A), substitution for lysine to glutaic acid at codon 542 of the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α (PIK3CA-E542K), substitution for histidine to arginine at codon 202 of the GNAS complex locus (GNAS-R202H), substitution for Lysine to termination codon at codon 1370 of the APC regulator of WNT signaling pathway (APC-K1370*), substitution for aspartic acid to glycine at codon 245 of the TP53 (TP53-G245D), substitution for serine to glycine at codon 245 of the TP53 (TP53-G245S) and non-frameshift deletion mutations from codon 117 Proline to codon 182 Cysteine of the tumor protein P53 (TP53-P177_C182del) were found in the analysis of tumor targeting/drug resistance-related variant genes. Considering that KRAS and TP53 had gene mutations, but other immunotherapy-related genes exhibited no change, antiangiogenic targeted therapy and chemotherapy drugs should be used but not immunotherapy (16).

The final diagnosis for the patient was rectosigmoid junction adenocarcinoma (T2N0M0 stage I) and precancerous colon polyps. According to the above results, the patient was

next treated with chemotherapy and targeted therapy to prevent tumor recurrence. The therapeutic schedule was bevacizumab 300 mg day (D) 1 (IV drip), irinotecan hydrochloride 100 mg D1 (IV drip) and capecitabine (1.5 g per os bid) D1-D14. A total of four cycles of the above-mentioned regimen were used, with treatments repeated every 3 weeks. During follow-up for 8 months, the patient was managed by regular review of blood routine and tumor markers and followed up by phone and by appointment, and the results showed that no tumor recurrence was found and CEA decreased continuously to the normal level, and the level of WBC, CRP, RBC and HGB also became normal in July 2023.

Discussion

In the present study, a noteworthy bicentric lesion case was described, with an early-stage COAD combined with precancerous colon polyps, which was treated with low-dose and short-course prophylactic adjuvant therapy. This special case and the corresponding therapy could guide clinical drug use in the future. Furthermore, the patient presented with a post-operative fever. Through investigation in all aspects, the cause of the patient's postoperative fever was identified as anemia with deep wound dehiscence secondary infection. The present study provides a feasible treatment idea for the clinical solution of postoperative complications.

Postoperative fever is a common symptom in CC patients with the underlying causes being infection, anemia, anastomotic leakage, and drug side effects (17,18). Usually, inflammation-induced postoperative fever presents as a high fever, with shallow wound incisional dehiscence, suppuration, fat liquefaction and other clinical manifestations (17,18), and postoperative fever caused by anemia is a low fever with a body temperature <38°C (19). In the present study, the patient's body temperature increased continuously to range 37.8-38.6°C, which was between low and high fever; furthermore, the WBC count and CRP both increased, which are indicators of inflammation. Thus, the patient of the present study was given antibiotics, such as amoxicillin for anti-inflammation and XueBiJing injections to dispel blood stasis and for detoxification. In addition, the patient received transfusion therapy, in which the erythrocyte suspension filtered from white blood cells from a healthy donor was injected into the patient to treat anemia. Subsequently, the patient's body temperature decreased to a range of 36.4-37.5°C, and in addition, the WBCs and level of CRP decreased. Finally, the reason for postoperative fever was found to be that the upper end of the patient's surgical incision was split to the anterior rectus abdominis sheath with a depth of 1.5 cm and a length of 2.5 cm when the suture was removed on the 10th postoperative day, leading to secondary infection. The split incision as well as fat liquefaction was noted 3 days after the suture had been removed. This could explain why the patient had a persistently higher body temperature and level of WBC and CRP, although the incision healed well. It was finally concluded that the reasons were anemia with deep wound dehiscence and secondary infection.

For the treatment of early-stage COAD, researchers advised that middle-aged patients with stage I disease receive postoperative chemotherapy (20,21). Traditional

Chinese medicine or other auxiliary therapies can inhibit the recurrence or even canceration of colon polyps, particularly precancerous polyps (22). However, to the best of our knowledge, there are few reports of bicentric lesions of early-stage COAD and precancerous colon polyps, and whether to use adjuvant therapy is still controversial. In this case, the patient not only had a bicentric lesion, but also had mutations in the genes KRAS, PIK3CA, GNAS, APC and TP53. Thus, the patient was given low-dose and short-course bevacizumab combined with hydrochloride and capecitabine after the operation.

Although the etiology of postoperative fever was finally confirmed in this case and prophylactic adjuvant therapy was given, the study has several limitations. First, the patient's anemia should have been corrected preoperatively. Second, abdominal ultrasonography should have been performed to determine whether deep wound dehiscence and secondary infection had occurred. Third, detailed preoperative colonoscopy and detailed medical communication between doctors are crucial. At last, the long-term outcome of postoperative low-dose and short-course adjuvant therapy is still unclear.

In conclusion, the cause of the patient's postoperative fever was anemia with deep wound dehiscence and secondary infection. Low-dose and short-course prophylactic adjuvant therapy is feasible for early-stage COAD with precancerous colon polyps.

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Availability of data and materials

The WES data generated in the present study may be found in the Mendeley Data database at the following URL: (https://data.mendeley.com/datasets/jmtpwdb6vv/1). The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MYW and XBZ wrote and revised the manuscript. SXZ, YY, ZMG, MYW and XBZ initiated and designed the project. XXF, LJ, HBZ, BXT, YJL, JCZ and LYS collected and organized all data. MYW, JLL and YFW drew and analyzed the images. All authors reviewed and edited the manuscript. All authors have read and approved the final manuscript. YY and SXZ checked and confirmed the authenticity of the raw data.

Ethics approval and consent to participate

Ethics approval was provided by the Ethics Committee of Dongzhimen Hospital Affiliated of the Beijing University of Chinese Medicine (Beijing, China; approval no. 2023DZMEC-048).

Patient consent for publication

Written informed consent was obtained from the patient for the publication of their clinical details and images.

Competing interests

The authors declare that they have no competing interests.

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