Infectious Agents and Cancer

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Case report: is necrotizing fasciitis in a rectal cancer patient after targeted systemic therapy related to the tumor site? - evidence from a hepatocellular carcinoma patient

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Abstract

Necrotizing fasciitis (NF) is a rare and life-threatening serious infectious disease, characterized by acute onset and rapid progress, leading to extensive necrosis of skin, soft tissue as well as fascia by a variety of aerobic and anaerobic bacteria, localized on external genitalia, scrotum, groin and perianal areas in males. There exist numerous common etiologies for NF, yet NF induced by malignant neoplasms is exceedingly rare. Several studies have reported that NF may be associated with tumor site (rectal/sigmoid colon cancer) and blood supply dysfunction caused by targeted therapy drugs (bevacizumab, aflibercept, ramucirumab). The perforation of colorectal cancer poses a unique risk factor for NF. However, in our two cases, the patient with rectal cancer received CapeOX (oxaliplatin + capecitabine) + bevacizumab + tislelizumab for 3 cycles without perforation but did develop NF. One month after debridement, the patient continued immunotherapy with tislelizumab alone for the fourth cycle and maintained for an additional 3 cycles without any recurrence of NF. Therefore, does the occurrence of NF correlate with the tumor site (rectum) and targeted immunotherapy? Another patient with hepatocellular carcinoma also developed NF after receiving 2 cycles of lenvatinib + sintilimab treatment. The third cycle of sintilimab immunotherapy was administered on the 13th day after operation, which was subsequently maintained for an additional 2 cycles without recurrence of NF. The absence of a direct correlation between hepatocellular carcinoma and rectal tumor location as well as immunotherapy, suggests that NF may be closely linked to targeted therapy.

Keywords Rectal cancer, Hepatocellular carcinoma, Necrotizing fasciitis, Fournier's gangrene, Bevacizumab, Lenvatinib

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Background

NF is an acute suppurative infection characterized by acute onset, rapid progression, and severe pain. Failure to promptly initiate treatment can potentially lead to sepsis and septic shock, thereby posing a grave threat to the lives of patients. NF, clinically rare but rapidly disseminating, is primarily witnessed in males, invading the skin, subcutaneous tissue, and both superficial and deep fascia. Its most characteristic manifestation is called Fournier's gangrene, a term coined by Jean Alfred Fournier in 1883 [1], which manifests with erythema, pain, localized swelling, and fever in the perianal, perineal as well as scrotal regions. There exist numerous high-risk factors for NF, encompassing diabetes, liver cirrhosis, alcoholism, malignant tumors, immunosuppression, chemotherapy-induced neutropenia, intravenous drug abuse, glucocorticoids, HIV, malnutrition, recent surgery and trauma, advanced age (age > 60 years), smoking, obesity, autoimmune diseases as well as renal insufficiency [2, 3]. Notably, NF caused by malignant tumors is exceedingly rare, specifically rectal cancer induces NF at an incidence rate ranging from 1.47–16.6% [4], while no reported incidences of NF related to hepatocellular carcinoma exist in literature. Considering the anatomical proximity between the lesion site around the anus and rectum region, it is reasonable to speculate that tumor site (rectal/sigmoid colon cancer) may be implicated in the occurrence of NF. Furthermore, the primary treatment of tumors include chemotherapy, targeted and immunotherapy. Are these treatments associated with NF? Limited literature reports exist on NF or Fournier's gangrene in patients with rectal cancer and hepatocellular carcinoma who have undergone chemotherapy and/or targeted therapy both domestically and internationally [5–9] (Table 1), which suggest that NF or Fournier's gangrene may be an adverse event related to antiangiogenic drug treatment for malignant tumors. However, there are no reports about NF in patients with rectal cancer and hepatocellular carcinoma after receiving targeted and immunotherapy. Here, we report a case of rectal cancer accompanied by NF after 3 cycles of CapeOX (oxaliplatin + capecitabine) + bevacizumab + tislelizumab treatment; During the same period, a patient with hepatocellular carcinoma also developed NF after 2 cycles of treatment with lenvatinib + sintilimab. Despite the critical condition of two patients, successful infection control was achieved through prompt and thorough surgical debridement, appropriate administration of broad-spectrum antibiotics, as well as active symptomatic supportive treatment. Subsequently, both patients discontinued targeted therapy and merely received immunotherapy. The wounds healed favorably, and no recurrence of NF was discerned. Therefore, we hypothesize that NF might be associated with targeted therapy rather than the tumor site or immunotherapy, as detailed below.

Case presentation

Case 1

A 48-year-old male patient was admitted to our hospital due to "anal itching for 2 years and difficulty in defecation for 1 week". Abdominal enhanced CT scan revealed uneven thickening of the intestinal wall extending from

Table 1 Summary of studies on necrotizing fasciitis or Fournier's gangrene in patients with rectal cancer or hepatocellular carcinoma after receiving chemotherapy and/or targeted treatment

Case	Author	Year	Age (years)	Sex	Diagnosis	Drug Use	Outcome	Treatment	Prognosis
1	Gamboa [5]	2010	67	Male	Resected colorectal cancer	mFOLFOX6+ bevacizumab	Fournier's gangrene	Antibiotics, surgical debridement, right orchiectomy, skin grafts	Unknown (discharged 28 days after admission)
2	Sendur [6]	2014	49	Female	Metastatic rectal adenocarcinoma	FOLFIRI+ bevacizumab	Necrotizing fasciitis	Ultrasonography-guided drainage of the abscess, antibiotics	Died due to the refractory septic shock on the 7th day of the antibiotic treatment
3	Ugai [7]	2014	59	Female	Rectal cancer	Fluorouracil+ irinotecan + bevacizumab	Necrotizing fasciitis	Antibiotics, surgical debridement	Died of metastatic colorectal cancer 6 months after discharge
4	Gonzaga [8]	2017	64	Male	Stage IV RAS wild-type rectosigmoid adenocarcinoma	FOLFIRI+ aflibercept	Fournier's gangrene	Abscess resection and debridement, antibiotics	Died 11 months after the diagnosis of Fournier's gangrene
5	Kang [9]	2019	57	Male	HBV-related hepatocellular carcinoma	Sorafenib	Necrotizing fasciitis	Antibiotics, surgical debridement, secondary wound suture	Unknown (discharged on the 23rd postoperative day)

the lower rectum to the anus, accompanied by intestinal stenosis, considered to be rectal cancer (Fig. 1A-B). Electronic colonoscopy showed ulcerative protrusion lesions located 1 cm away from the anal with a diameter of approximately 5 cm and circumferential growth, resulting in significant lumen stenosis and deformation (Fig. 1C-D). Pathological examination confirmed moderately differentiated adenocarcinoma of rectum with clinical stage $T_4N_1M_X$. Eastern Cooperative Oncology Group (ECOG) score: 1 point; Karnofsky score: 80 points; Visual Analogue Scale (VAS) score: 6 points; Nutritional Risk Screening (NRS) score: 3 points. Serum tumor markers tests were as follows: CEA:14.40ng/mL (0-3.4ng/mL), CA199:28.50U/mL (0-27U/mL), CA72-4:11.50U/mL (0-6.9U/mL), CY211:8.53ng/mL (0-3.3ng/mL), ProGRP:26.2pg/mL (28.3-74.4pg/mL). Genetic test results indicated KRAS Exon-2 gene mutation. Notably, the patient exhibited normal cardiac, hepatic, pulmonary, and renal functions without prior medical history of hypertension, diabetes mellitus, or coronary artery disease. After a comprehensive evaluation by our multidisciplinary team (MDT), neoadjuvant therapy was ultimately determined, which included the placement of an indwelling rectal stent (90 mm×22 mm, 41390A03, Boston) for alleviating symptoms associated with intestinal obstruction, as well as the administration of the CapeOX (oxaliplatin + capecitabine) + bevacizumab + tislelizumab regimen. Oxaliplatin 130mg/m^2, d1, ivgtt; capecitabine 1000mg/m^2, bid, d1-d14, po; bevacizumab 7.5 mg/kg, d2, ivgtt; tislelizumab 200 mg, d2, ivgtt, in each treatment circle lasting for 3weeks.

After 3 cycles of treatment, the patient had a sudden onset of perianal pain and discomfort, which gradually spread to the entire gluteal, scrotal as well as inguinal regions, accompanied by localized redness, swelling, high skin temperature, and incontinent dermatitis changes in the inguinal and perianal areas. The patient's body temperature was 39.5℃, pulse rate was 115beats/min, respiratory rate was 20beats/min, and blood pressure was 115/75mmHg. Complete blood count (Fig. 2A): WBC: 22.3×10^9/L, NE%: 92%, RBC: 3.54×10^{12}/L, Hb: 101 g/L, PLT: 223×10^9/L; Blood biochemistry(Fig. 2B): ALB: 27.7 g/L, A/G: 0.85, GLU: 2.83mmol/L; Infection indicators (Fig. 2C): PCT: 4.53ng/mL, IL-6: 4187pg/mL; Coagulation function examination (Fig. 2D): PT: 16.5s, APTT: 34.9s, FIB: 6.61 g/L, INR: 1.52, Dimer: 2.8 μg/mL. Rectal scanning and enhanced MRI (Fig. 3) revealed large-scale soft tissue pneumatization as well as exudation in the abdominal wall, buttocks, and perineum. Additionally, nodules were observed in the posterior wall of the rectum near the anus after rectal cancer stenting without any signs of rectal perforation. The preliminary diagnosis was as follows: (1) rectal malignancy; (2) perianal abscess; (3) necrotizing fasciitis; (4) hypoproteinemia; (5) coagulation dysfunction.

After the consultation in the ultrasound department prior to the surgery, perianal abscess puncture catheter drainage was performed immediately (Fig. 4A), followed by bacterial and fungal culture as well as drug sensitivity testing of the drained pus. To combat infection, the patient was temporarily treated with broad-spectrum antibiotics consisting of levofloxacin and ornidazole. During preoperative preparation, on May 27, 2022, there

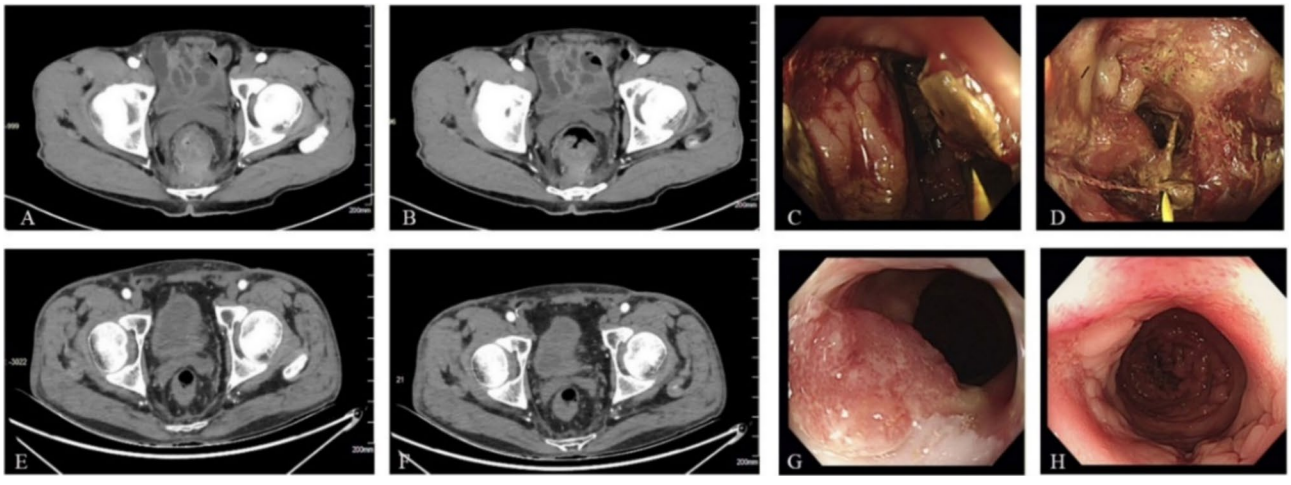

Fig. 1 Enhanced CT and electronic colonoscopy examination results of the rectal cancer patient before and after treatment. (**A**, **B**) Enhanced CT before treatment showed uneven thickening of the intestinal wall extending from the lower rectum to the anus, accompanied by intestinal stenosis. (**C**, **D**) Electronic colonoscopy before treatment showed ulcerative protrusion lesions located 1 cm away from the anal with a diameter of approximately 5 cm and circumferential growth, resulting in significant lumen stenosis and deformation. (**E**, **F**) Enhanced CT at 3.5 months post-surgery exhibited reduced thickness of the intestinal wall from the lower rectal to the anus. (**G**, **H**) Electronic colonoscopy at 3.5 months post-surgery indicated shrinkage of the ulcer lesion located 1 cm from the anal opening, presenting a granular surface with a maximum diameter of about 1.5 cm

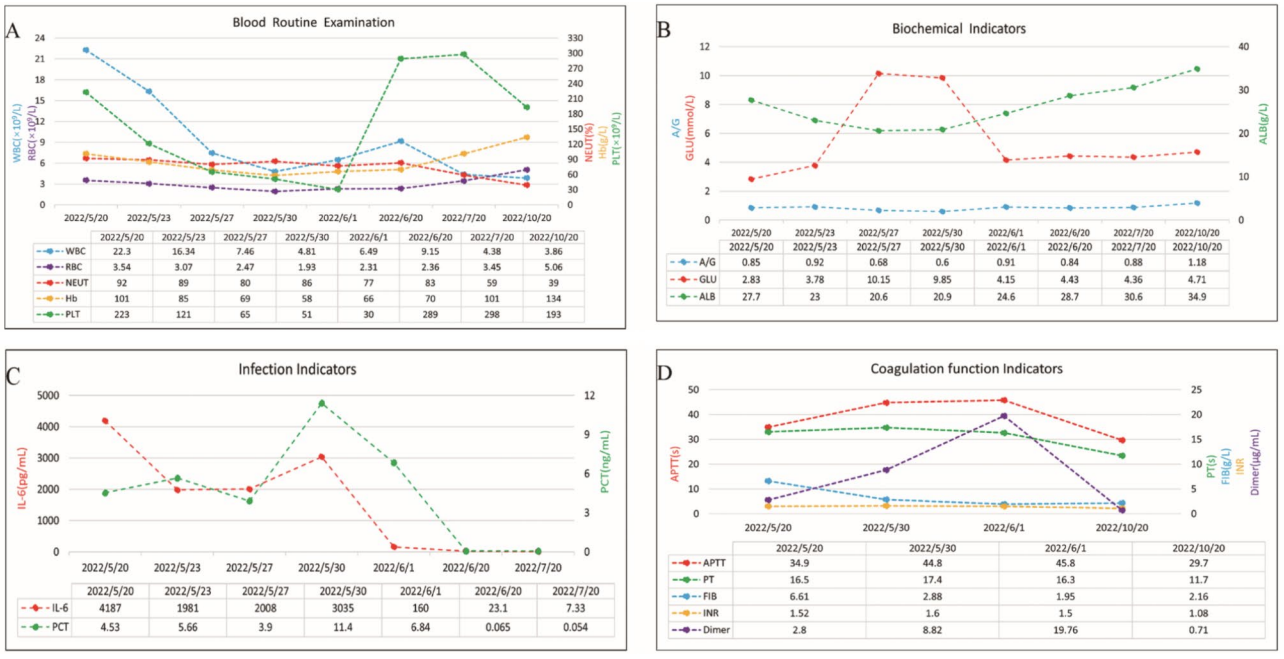

Fig. 2 Laboratory examination results of the rectal cancer patient. (**A**) Complete blood count; (**B**) Blood biochemical examination; (**C**) Infection indicators; (**D**) Coagulation function examination

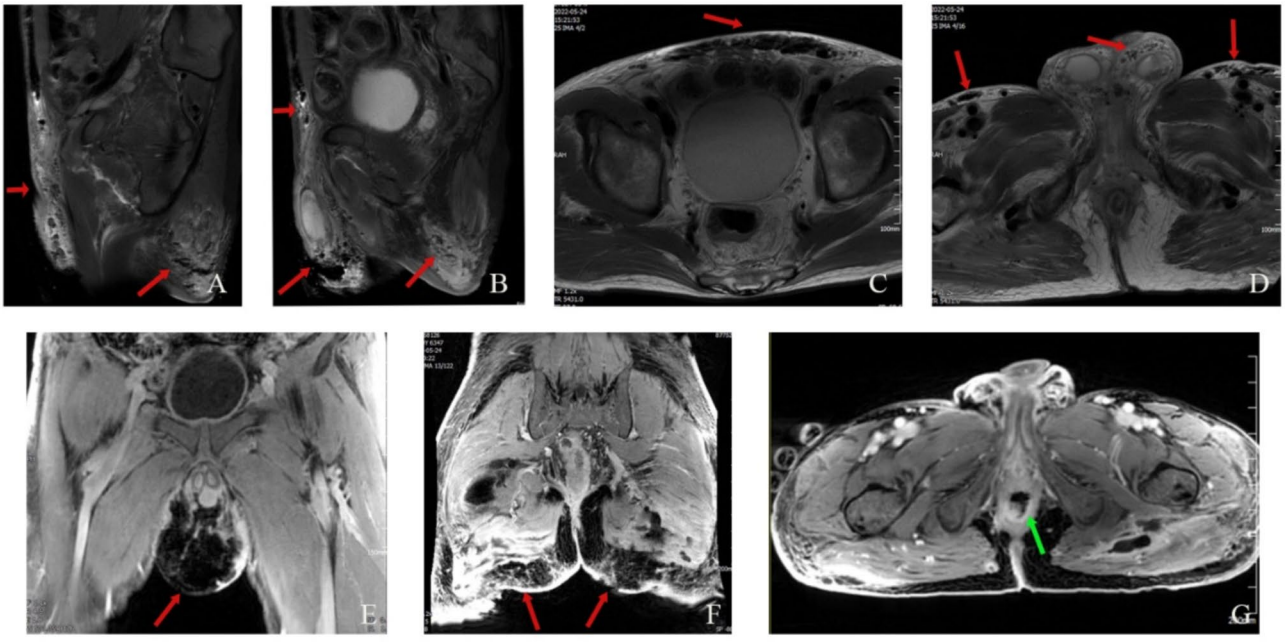

Fig. 3 Representative images of MRI for the rectal cancer patient. (**A**, **B**) Sagittal, (**C**, **D**) axial and (**E**, **F**) coronal images of MRI showing large-scale soft tissue pneumatization as well as exudation in the abdominal wall, buttocks, and perineum. (**G**) Nodules on the posterior wall of the rectum adjacent to the anus, without evidence of rectal perforation

was a spontaneous rupture of the perianal abscess with a copious discharge of pus, accompanied by progressive subcutaneous gas accumulation and fever. Consequently, under general anesthesia, perianal necrotizing fasciitis debridement and perianal abscess incision and drainage were performed to remove the primary lesion (Fig. 4B). The bacterial and fungal cultures revealed the presence of Escherichia coli and Streptococcus viridans as the causative agents of infection. Drug susceptibility testing demonstrated sensitivity to third generation cephalosporins, levofloxacin, imipenem, and vancomycin, while blood culture yielded negative results. Consequently, the

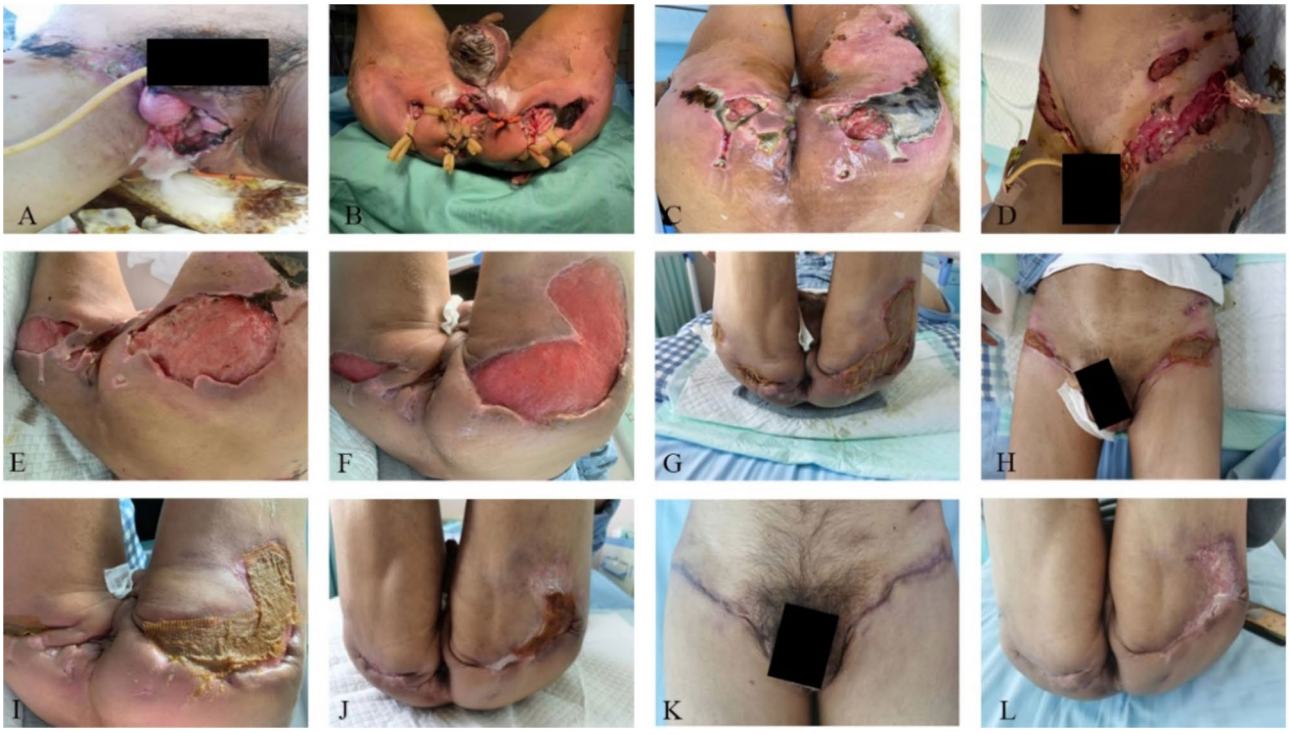

Fig. 4 Local changes of infected lesions in the patient with rectal cancer. (**A**) The initial debridement revealed multiple ulcers in the perineum, scrotum, and inguinal region accompanied by copious malodorous purulent secretions. (**B**) Following debridement of perianal necrotizing fasciitis, four radial incisions were observed on the left and right buttocks, respectively, along with the placement of silicone tubes for paired drainage between the incisions. (**C**, **D**) On the 10th day post-surgery, extensive damage to the skin of bilateral buttocks, thighs and inguinal areas was evident along with abundant malodorous purulent secretions and gangrene formation in certain areas of the buttocks and thighs. (**E**) By postoperative day 18, there was a reduction in purulent secretions from the damaged skin of both buttocks and thighs. (**F**) One month after surgery, wounds on both sides exhibited a ruddy appearance with minimal chylous secretions. (**G**, **H**, **I**) Two months later, povidone-iodine gauze covered the surface of bilateral thighs, buttocks, and inguinal regions with local granulation tissue growth. (**J**) At 3.5 months post-surgery, extensive granulation tissue covered the wounds on both buttocks and thighs. (**K**, **L**) 5 months postoperatively, the wounds on bilateral inguinal regions as well as those on the buttocks and thighs healed well exhibiting fresh ruddy granulation tissue

antibiotic treatment regimen was adjusted to ceftriaxone plus ornidazole. On the 3rd day post-surgery, the patient was transferred to the intensive care unit (ICU) for rescue treatment owing to a combination of respiratory alkalosis and metabolic acidosis, hyperlactacidemia, septic shock, as well as septic encephalopathy. After transfer, the patient received intensive care while the antibiotic treatment regimen was adjusted to meropenem plus vancomycin. One month after surgery, only the fourth cycle of tislelizumab immunotherapy was administered to the patient who continued with three additional cycles without any recurrence of NF. At three and a half months post-surgery, significant reduction in size of rectal cancerous lesions compared to before can be observed (Fig. 1E-H). Five months following operation, satisfactory wound healing with improved ambulation was noted. The progress of postoperative wound recovery is depicted in Fig. 4C-L. The patient's condition remained satisfactory until March 20th, 2024.

Case 2

A 60-year-old man was presented to the hospital with complaints of right upper abdominal distension and pain with fatigue for half a month. Abdominal enhanced CT revealed a large space-occupying lesion in the right lobe of the liver with multiple foci, measuring approximately 11.9 cm in maximum diameter, suggestive of mixed hepatocellular carcinoma. Additionally, tumor thrombus was observed in the right branch and main portal vein, along with multiple enlarged lymph nodes in the retroperitoneum and mesentery. Decompensated stage signs of liver cirrhosis were evident, including portal hypertension, splenomegaly, esophageal and gastric varices, as well as ascites. Later liver biopsy was confirmed moderately differentiated hepatocellular carcinoma. Immunohistochemical (IHC) staining demonstrated cancer cells: Glypican-3 (+), Hepatocyte (+), CD34 (sinus (+)), CEA (-), CK7 (-), CK20 (partial (+)), AFP (+), CK19 (-), CKp (+), Arg-1 (-), GS (partial (+)), HSP70 (+), Ki67 positive cells (60%+), and tumor markers tests were abnormal, AFP: 53.3ng/mL(0-7ng/mL), CA125: 286U/mL(0-35U/

mL), NSE:82.4ng/mL (0-20.46ng/mL), CY211:4.97ng/mL(0-3.3ng/mL). The electronic gastroduodenoscopy indicated mild esophageal varices, hemorrhagic gastritis, and chronic inflammation of the gastric antrum mucosa with acute inflammatory activity (neutrophil+). The electronic colonoscopy unveiled no abnormalities in the ileum and colorectal. Moreover, the patient's Karnofsky score, 60 points, ECOG score, 2 points, VAS score, 7 points, and NRS score, 4 points. He had a history of hepatitis B virus for over 20 years and was taking entecavir capsules (0.5 mg, po, qd) for anti-HBV therapy. The five tests conducted for HBV revealed the following results: HBsAg>130IU/mL, Anti-HBs:10.6mIU/mL, HBeAg:213 S/CO, and high-sensitivity quantitative analysis of HBV DNA indicated viral replication (GHBV-DNA=3.37E+6). Additionally, liver fibrosis biomarkers were assessed as follows: PC-III:54ng/mL, LN:215ng/mL, IV-C:259ng/mL, HA:125ng/mL. The patient's liver function was classified as Child-Pugh C; however, their heart, lung and kidney functions were essentially normal in nature. Importantly to note is that the patient explicitly denied any medical history pertaining to hypertension, diabetes or coronary heart disease. Following extensive and rigorous discussion by the MDT, it was collectively determined that the patient would undergo FOLFOX (oxaliplatin+leucovorin calcium+5-fluorouracil) hepatic arterial infusion chemotherapy (HAIC) in combination with lenvatinib and sintilimab regimen. Oxaliplatin 85mg/m^2, d1, ivgtt; leucovorin calcium 400mg/m^2, d1, ivgtt; 5-fluorouracil 400mg/m^2, 0–2 h, d1, iv, 1200mg/m^2/d, d1-d2, ivgtt; lenvatinib 8 mg, po, qd; sintilimab 200 mg, ivgtt, with 21 days as a treatment cycle. Considering the patient's impaired hepatic function and utilization of peritoneal puncture drainage owing to extensive ascites, only a combination of targeted therapy (lenvatinib, 8 mg, po, qd) and immunotherapy (sintilimab, 200 mg, ivgtt) was administered during the second treatment cycle. After undergoing two cycles of treatment, the patient experienced sudden and excruciating pain in the perianal and left inguinal regions. Physical examination revealed that an approximately 2×1 cm excrescence could be seen at the anal opening, along with redness, swelling, heat and pain in the perianal, scrotum as well as left inguinal region. Additionally, fistulas measuring approximately 5×4 cm and 4×3 cm were observed in the left perianal and left inguinal regions (Fig. 5A-B), accompanied by exudation of bloody fluid and yellow purulent secretion. Ultrasound examination (Fig. 6) demonstrated mixed echoes measuring about 4.4×1.1 cm in the left perianal region, exhibiting an irregular shape with indistinct boundaries. Additionally, interconnected mixed echoes measuring approximately 1.9×0.5 cm were detected in the deep fat layer, indicating perianal abscess along with localized sinus formation. The patient's vital signs showed T36.5 °C, P74beats/min, R19beats/min, BP111/64mmHg. His white blood cell count was 5.58×10^9/L (with 81% neutrophils), and platelet count was 50×10^9/L (Fig. 7A). Liver function tests (Fig. 7B): TBil: 99.6μmol/L, DBil: 62μmol/L, IBil: 37.6μmol/L, ALT: 25U/L, AST: 66U/L; Blood biochemistry (Fig. 7C): ALB: 15.5 g/L, A/G: 0.41, GLU: 3.03mmol/L; Infection indicators (Fig. 7D): PCT: 2.34ng/mL, IL-6: 236pg/mL; Serum ammonia ($NH_{3)}$ (Fig. 7E): 39.2μmol/L; Coagulation function examination (Fig. 7F): PT: 20.1s; APTT: 47.6s, FIB: 1.66 g/L; INR: 1.8; Dimer: 4.19 μg/mL. The initial diagnosis was as follows: (1) hepatic malignancy; (2) perianal abscess; (3) necrotizing fasciitis; (4) hepatitis B virus infection; (5) decompensated liver cirrhosis; (6) portal hypertension; (7) splenomegaly; (8) gastric fundus esophageal varices; (9) hepatic encephalopathy; (10) hypoproteinemia; 11. thrombocytopenia; 12. coagulation dysfunction; 13. ascites.

The wound secretion was subjected to bacterial and fungal culture, which confirmed the presence of Klebsiella pneumoniae infection. Drug sensitivity testing revealed susceptibility to third generation cephalosporins, ciprofloxacin, gentamicin, and imipenem. Consequently, ceftazidime was administered as an appropriate anti-infection treatment. The patient presented with an enlarged perianal and scrotal inflammation, along with an expanded left perianal and left inguinal fistula, accompanied by a substantial discharge of yellow malodorous pus on June 21, 2022. As a result of unsatisfactory conservative treatment, surgery involving incision and drainage of the perianal abscess was conducted under general anesthesia. Following meticulous debridement and dressing changes, remarkable reduction in perianal inflammation was observed after 12 days post-operation, leading to removal of the inguinal abscess drainage tube. The third cycle of sintilimab immunotherapy was administered on postoperative day 13, which was continued for two subsequent cycles, without experiencing any recurrence of NF. By August 16, 2022, the incision had completely healed (Fig. 5C-D). Follow-up until October 20, 2022, the patient died due to complications of liver failure and hepatorenal syndrome.

Discussion and conclusion

NF, a carnivorous disease, was initially proposed by Wilson in 1952 [10]. It is an acute soft tissue infection characterized by necrosis of the skin and fascia caused by various bacteria that spread through the subcutaneous fascial space, leading to tissue ischemia and subcutaneous artery thrombosis. NF exhibits an insidious onset with an incidence rate ranging from (1.6–3.3)/100,000 [11], and a mortality rate as high as 35% [12]. Delayed or inadequate diagnosis and treatment may progress into sepsis, multiple organ dysfunction syndrome (MODS),

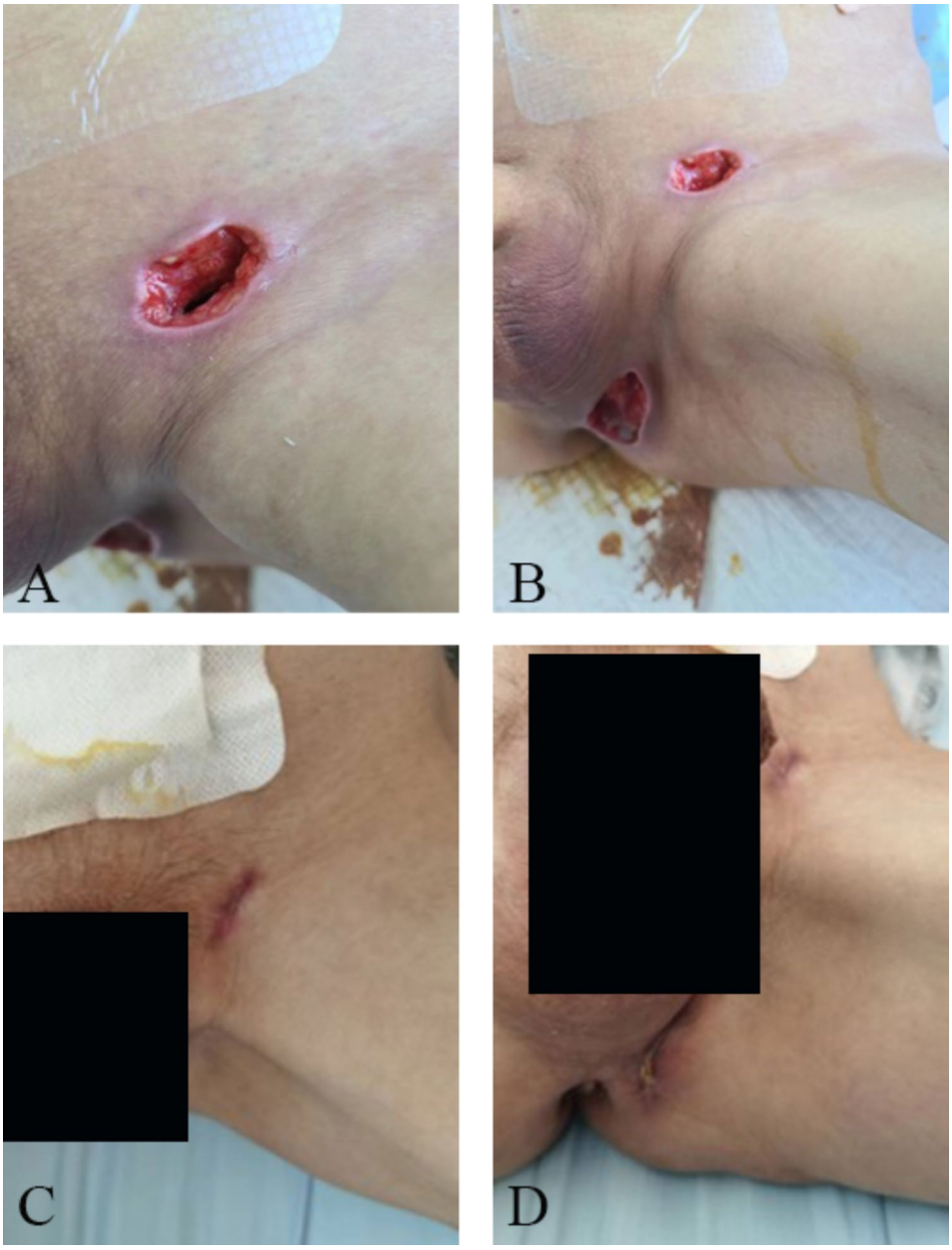

Fig. 5 Local changes of infected lesions in the patient hepatocellular carcinoma. (**A**, **B**) Fistulas measuring approximately 5×4 cm and 4×3 cm were observed in the left perianal and inguinal areas, respectively. (**C**, **D**) The ulcers in the left perianal and inguinal areas exhibited complete healing, leaving behind two visible scars

or even fatality. Early surgical debridement combined with the judicious use of broad-spectrum antibiotics and active symptomatic treatment can significantly mitigate the risk of mortality in patients.

NF in oncological patients has been depicted as being associated with the tumor site (rectal/sigmoid colon cancer), targeted therapeutic drugs that induce local tissue necrosis through disrupting blood supply (bevacizumab, aflibercept, ramucirumab), and factors that augment the risk of infection (diabetes, cirrhosis, alcoholism, recent surgical trauma). In our two cases, NF occurred after completion of 3 cycles of CapeOX (oxaliplatin + capecitabine) + bevacizumab + tislelizumab treatment in a patient with rectal cancer who had no prior history of smoking, alcohol, or diabetes, and who had not undergone recent surgery or injury. Perforation of colorectal cancer is a particular risk factor for NF, especially in low rectal cancer. The possible cause is the necrosis and shedding of tumor tissue surface mucosa near the dentate line, which, when mixed with feces, can easily lead to anorectal gland infection, thereby resulting in abscess formation and even spontaneous perforation

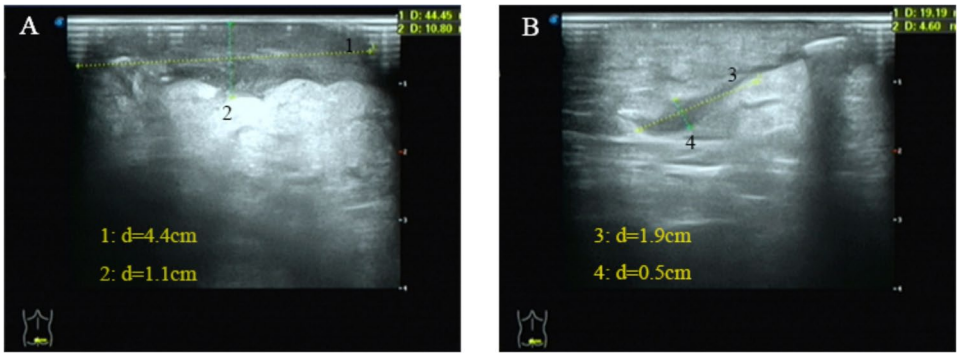

Fig. 6 Ultrasonographic findings of the hepatocellular carcinoma patient. (**A**) Heterogeneous echoes with irregular morphology and indistinct margins were observed in the left perianal region measuring approximately 4.4 × 1.1 cm. (**B**) Mixed echoes were identified within the deep adipose layer measuring around 1.9 × 0.5 cm

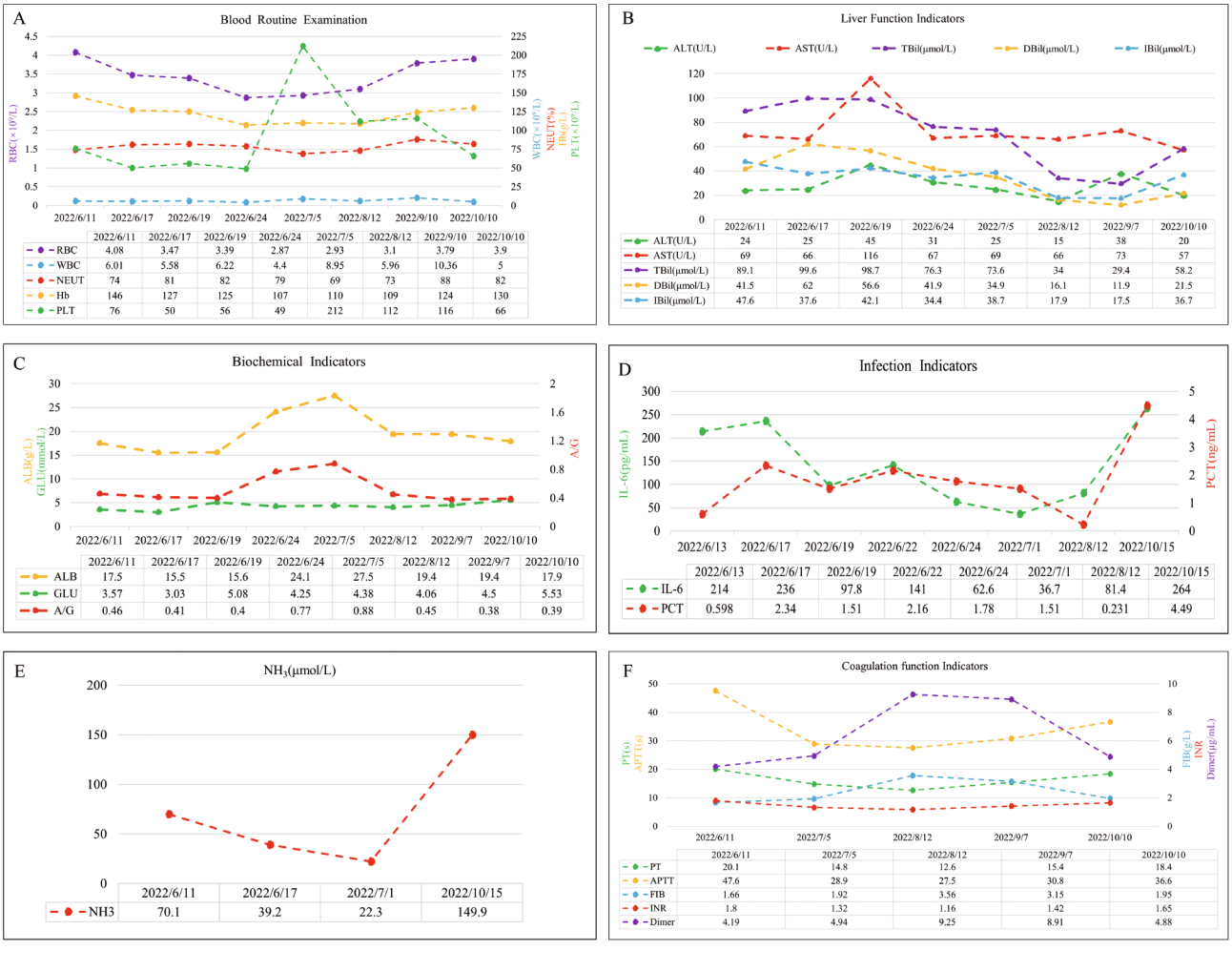

Fig. 7 Laboratory examination results for the hepatocellular carcinoma patient. (**A**) Complete blood count; (**B**) Liver function tests; (**C**) Blood biochemical examination; (**D**) Infection indicators; (**E**) Serum ammonia; (**F**) Coagulation function examination

through spreading and infiltration. Furthermore, there exist literature reports indicating that bevacizumab has the potential to induce rectal cancer perforation, with an incidence rate of 1.3% [13]. However, imaging evidence revealed the absence of perforation in this patient, suggesting that the occurrence of NF might not be associated with the tumor site but rather the use of target-immunity drugs. Following surgery, the patient only received 4 cycles of tislelizumab treatment without experiencing any recurrence of NF, indicating that NF

may be irrelevant to immunotherapy but rather associated with targeted therapy. The patient, diagnosed with liver cirrhosis and hepatocellular carcinoma, had a 20-year history of HBV but denied any history of hypertension, diabetes, drinking and smoking. Since there is no relationship between hepatocellular carcinoma and rectal tumor location, the patient also developed NF after receiving two cycles of lenvatinib plus sintilimab, indicating that NF may be related to targeted and immunotherapy. Afterwards, the patient discontinued lenvatinib and received 3 cycles of immunotherapy with sintilimab. At 2-month follow-up visits, this patient's incision healed well without recurrence of NF, thereby providing conclusive evidence that NF was unrelated to immunotherapy but to targeted therapy.

Bevacizumab, the first recombinant humanized IgG1 monoclonal antibody targeting vascular endothelial growth factor (VEGF) approved by the U.S. Food and Drug Administration (FDA), competitively inhibits the binding of vascular endothelial growth factor receptor (VEGFR) and VEGF, thereby suppressing tumor angiogenesis. Moreover, it exerts anti-tumor effects by inhibiting tumor growth and metastasis as well as inducing apoptosis of tumor cells. Nevertheless, one of the adverse reactions associated with anti-angiogenic drugs is arteriovenous thromboembolism [14]. Therefore, it is believed that bevacizumab induces thrombosis in blood-supplying vessels, resulting in tissue ischemia and necrosis, which in turn triggers NF. Additionally, bevacizumab may also impair wound healing and elevate the likelihood of bacterial infection, ultimately causing NF [15]. As early as 2010, several scholars reported that a 67-year-old male patient with metastatic colorectal cancer (CRC) who developed Fournier's gangrene during bevacizumab administration after completing 4 months of mFOLFOX6 (5-fluorouracil+leucovorin calcium+oxaliplatin) therapy [5]. In 2013, a 52-year-old female with advanced rectal cancer experienced severe NF following the second course of XELOX (capecitabine+oxaliplatin)+bevacizumab treatment [16]. Sendur et al. [6]. presented a case of NF developed in a patient with liver metastasis of rectal adenocarcinoma treated with the third cycle of FOLFIRI (5-fluorouracil+leucovorin calcium+irinotecan) combined with bevacizumab, and eventually succumbed to septic shock. Lenvatinib, an oral multi-targeted tyrosine kinase inhibitor (TKI), inhibits tumor angiogenesis as well as tumor cell proliferation, infiltration, invasion, and metastasis by blocking vascular endothelial growth factor receptors 1–3 (VEGFR1-3), platelet-derived growth factor receptor-α (PDGF-α), and fibroblast growth factor receptor 1–4 (FGFR1-4). Currently, only one case report has described Fournier's gangrene in an 80-year-old male patient with radioiodine-refractory metastatic thyroid cancer after 14 months of treatment with lenvatinib [17]. The adverse reactions associated with lenvatinib include hypertension, proteinuria, nephrotic syndrome, liver toxicity, cardiac dysfunction, hand-foot syndrome, arterial thromboembolism and gastrointestinal perforation. Therefore, NF or Fournier's gangrene is likely to be caused by the disruption of the coagulation cascade response caused by lenvatinib through the inhibition of the VEGF/VEGFR signaling pathway, which further leads to thrombosis of small blood vessels in the skin [18]. Thrombosis can disrupt tissue blood supply resulting in local tissue ischemia-hypoxia necrosis and secondary bacterial colonization thereby increasing the risk of NF.

In conclusion, should push clinicians, during periodic evaluation of cancer patients undergoing targeted therapy, to ask questions about inflammatory manifestations like erythema, edema, and pain emerge on the perianal, inguinal, as well as perineal skin, even accompanied by high fever, tachycardia, hypotension, extensive necrotic subcutaneous tissue and fascia, and strongly suspect NF. Once it occurs, immediate cessation of targeted therapy is imperative. In addition, given the fact that it has a high mortality rate, timely and thorough surgical debridement, early and accurate administration of broad-spectrum antibiotics, along with proactive symptomatic supportive therapy constitute pivotal measures for disease control, enhancement of patient survival rate and quality of life.

Abbreviations

NF	Necrotizing fasciitis
CT	Computed tomography
ECOG	Eastern cooperative oncology group
VAS	Visual analogue scale
NRS	Nutritional risk screening
CEA	Carcinoembryonic antigen
AFP	Alpha-fetoprotein
NSE	Neuron specific enolase
CA125	Carbohydrate antigen 125
CA199	Carbohydrate antigen 199
CA72-4	Carbohydrate antigen 72–4
CY211	Cytokeratin 19 fragment antigen 211
ProGRP	Pro-gaspin-releasing peptide
MDT	Multidisciplinary team
WBC	White blood cell
NE	Neutrophils
RBC	Red blood cell
Hb	Hemoglobin
PLT	Platelet
ALB	Albumin
A/G	Albumin: Globulin
GLU	Glucose
PCT	Procalcitonin
IL-6	Interleukin-6
PT	Prothrombin time
APTT	Activated partial thromboplastin time
FIB	Fibrinogen
INR	International normalized ratio
CK	Cytokeratin
CD	Cluster of differentiation
Arg-1	Arginase-1
HSP70	Heatshockprotein70
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
TBIL	Total bilirubin

DBIL	Direct bilirubin
IBil	Indirect bilirubin
NH_3	Serum ammonia
MRI	Magnetic Resonance Imaging
ICU	Intensive care unit
IHC	Immunohistochemical
HBV	Hepatitis B Virus
HIV	Human immunodeficiency virus
PC-III	Precollagen III peptide
LN	Laminin
IV-C	Collagen IV
HA	Hyaluronidase
HAIC	Hepatic arterial infusion chemotherapy
T	Temperature
P	Pulse
R	Respiration
BP	Blood pressure
MODS	Multiple organ dysfunction syndrome
IgG1	Immunoglobulin G1
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
FDA	Food and Drug Administration
PDGF-α	Platelet-derived growth factor receptor-α
TKI	Tyrosine kinase inhibitor

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Author contributions
Xiaowen Han: Conceptualization; Data curation; Formal analysis; Methodology; Investigation; Writing – original draft.Xiaodong Huang: Data curation; Formal analysis; Methodology. Jiayi Zhang: Data curation; Investigation; Methodology. Weidong Li: Formal analysis; Investigation; Visualization. Zhen Ma: Visualization; Investigation. Bin Ma: Investigation; Data Curation. Ewestse Paul Maswikiti: Visualization; Formal analysis. Zhenyu Yin: Validation. Yuhan Wang: Validation. Lei Gao: Data Curation. Hao Chen: Conceptualization, Funding Acquisition, Resources, Supervision, Writing - Review & Editing. All authors read and approved the fnal manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
No ethical committee approval was needed for this study. Written informed consent was obtained from the patients in this study.

Consent for publication
Informed consent for publication was provided by the participants.

Competing interests
The authors declare no competing interests.

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