



A fatal case of Fournier's gangrene during neoadjuvant radiotherapy for rectal cancer

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Abstract

Purpose To report the development of an ultimately fatal occurrence of Fournier's gangrene in a rectal cancer patient undergoing neoadjuvant radiotherapy without chemotherapy.

Methods A 53-year-old male patient with G2 cT3 cN1a cM0 stage IIIB adenocarcinoma of the lower rectum and several comorbidities including ulcerative colitis was treated with 56 Gy to the primary tumor in 28 fractions because he declined the recommended simultaneous chemotherapy. He was also enrolled in the ketogenic diet arm of our KETOCOMP study, so that prospective measurements of blood parameters, quality of life, and body composition were made.

Results The patient died 6 days after completion of radiotherapy due to septic shock associated with Fournier's gangrene reaching from the right buttock into the gluteal muscles and descending into the scrotum. In retrospect, there were several signs probably indicating the development of the gangrene: (i) a decline in bioelectrical phase angle; (ii) an accelerated weight and fat-free mass loss starting in the third week of radiotherapy; (iii) an increase in C-reactive protein (CRP) and concurrent drop in high-density lipoprotein (HDL) cholesterol and insulin-like growth factor (IGF)-1 concentrations; and (iv) the occurrence of a sharp pain in the perianal region reported in the fifth week of radiotherapy. Notably, his self-reported quality of life score was the same at the end of as before radiotherapy.

Conclusions This case highlights the occurrence of Fournier's gangrene as an extremely rare but life-threatening complication during neoadjuvant radiotherapy for rectal cancer which should be refreshed in the awareness of radiation oncologists and radiologists.

Keywords Bioimpedance analysis · Body composition · Grade V toxicity · KETOCOMP study · Ketogenic diet

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Entwicklung eines tödlichen Fournier-Gangräs während neoadjuvanter Bestrahlung eines Rektumkarzinoms

Zusammenfassung

Zielsetzung Bericht über die Entwicklung eines zum Tode führenden Fournier-Gangräs während neoadjuvanter Bestrahlung eines Rektumkarzinoms ohne Chemotherapie.

Methoden Ein 53-jähriger männlicher Patient mit einem Adenokarzinom des unteren Rektums im Stadium IIIB (G2 cT3 cN1a cM0) sowie mehreren Komorbiditäten, unter anderem einer Colitis ulcerosa, wurde wegen Ablehnung einer simultanen Chemotherapie neoadjuvant mit 56Gy in 28 Fraktionen bestrahlt. Zudem unterzog er sich gleichzeitig einer ketogenen Ernährungsintervention innerhalb unserer KETOCOMP Studie, so dass prospektive Messungen von Blutparametern, Lebensqualität und Körperzusammensetzung gemacht wurden.

Ergebnisse Der Patient verstarb 6 Tage nach der Strahlentherapie an einem septischen Schock im Zusammenhang mit einem ausgedehnten Fournier-Gangrän, welches sich von der rechten Gesäßhälfte, die Glutealmuskulatur infiltrierend, bis ins Skrotum erstreckte. Retrospektiv ergaben sich mehrere Hinweise auf die Entwicklung eines Gangräs: (i) eine Abnahme des bioelektrischen Phasenwinkels; (ii) eine beschleunigte Abnahme des Körpergewichts und fettfreier Masse ab der dritten Therapiewoche; (iii) ein Anstieg der C-reaktives Protein(CRP)-Konzentration bei gleichzeitiger Abnahme des High-density Lipoprotein(HDL)-Cholesterin- und dem Insulin-ähnlichen Wachstumsfaktor(IGF)-I-Spiegels; (iv) das Auftreten stechender perianaler Schmerzen beginnend ab der fünften Therapiewoche. Bemerkenswerterweise gab der Patient subjektiv die gleiche Lebensqualität am Ende wie zu Beginn der Strahlentherapie an.

Schlussfolgerung Auch wenn die Entwicklung eines Fournier-Gangräs eine extrem seltene Nebenwirkung neoadjuvanter Bestrahlung von Rektumkarzinomen darstellt, verdeutlicht dieser Fall die Ernsthaftigkeit derselben, der sich Radioonkologen und Radiologen bewusst sein sollten.

Schlüsselwörter Bioimpedanz-Analyse · Körperzusammensetzung · Grad V Nebenwirkung · KETOCOMP Studie · Ketogene Ernährung

Introduction

Fournier’s gangrene (FG) can be defined as “an infective necrotizing fasciitis of the perineal, genital or perianal regions,” where the “infective process leads to thrombosis of subcutaneous blood vessels, resulting in gangrene of the overlying skin” [1]. Mortality rates of FG range between 3 and 45%, with sepsis and organ failure being common causes of death [2]. Risk factors for FG include diabetes, smoking, alcoholic liver cirrhosis, renal insufficiency, and—more specifically—rectal cancer and cortisol enema-induced rectal perforation [3, 4]. Rectal cancer-induced FG is very rare; according to Pittaka et al. [5], only three cases of rectal cancer patients developing FG after receiving radiotherapy (RT) have been reported thus far. One of these developed FG two years after completion of RT, possibly due to chronic self-administration of hydrocortisone enemas [3]. Another three patients developing FG during RT are included in a compilation by Czymek et al. [6], in which the authors explicitly mention tissue damage from pelvic RT as a risk factor.

Here we report an ultimately fatal case of FG occurring in a rectal cancer patient undergoing neoadjuvant RT without concurrent chemotherapy. In retrospect, some early indications for the development of FG become apparent that

could be helpful to prevent future deaths due to this rare but severe complication of RT.

Case report

The 53-year-old male patient had been diagnosed with a biopsy proven, CT and MRI-staged, G2 cT3 cN1a cM0 stage IIIB adenocarcinoma of the lower rectum in January 2018. He was referred to our clinic for neoadjuvant radiochemotherapy with the goal of improving the chances of sphincter conserving R0 resection and local tumor control. His comorbidities included alcoholic liver cirrhosis, former smoking with 13.5 pack-years, chronic knee pain due to arthritis, and ulcerative colitis since about 21 years that was indolent at the time of presentation. At first consultation he reported weight loss of 4 kg within the previous 3 months, bloody stools, and general weakness; prior blood tests had shown signs of anemia (hemoglobin levels in the range 7–9 g/dl). Because of his comorbidities, the patient refused to undergo the recommended simultaneous chemotherapy, but he was very interested in supportive dietary treatment options. Accordingly, he was offered to participate in the ketogenic diet arm of the KETOCOMP study (ClinicalTrials.gov Identifier no. NCT00123456 [7]), which he consented to. The study was approved by the

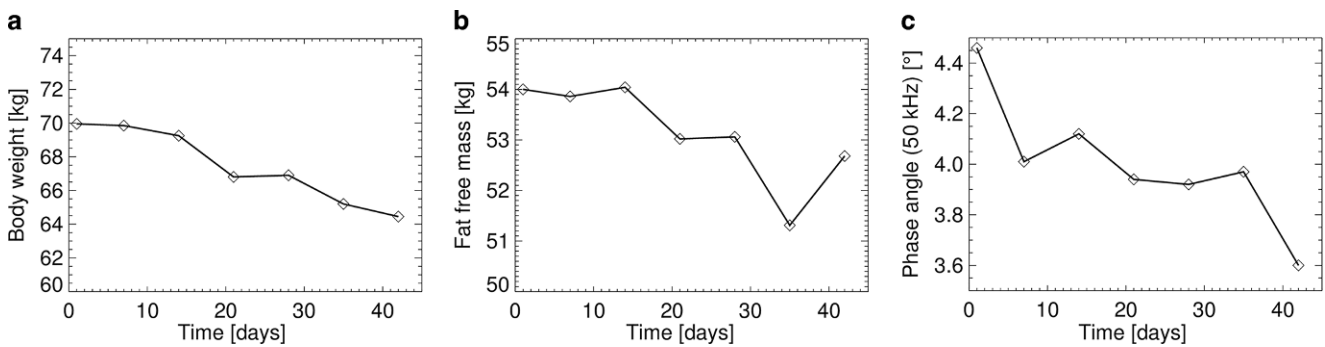


Fig. 1 Development of body weight (a), fat-free mass (b), and bioelectrical phase angle at 50 kHz (c) during the course of radiotherapy.

ethics committee of the Bavarian Medical Association (Bayerische Landesärztekammer), and all treatments were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. RT was planned for 25 fractions of 1.8 Gy to the planning target volume (measuring 1791.7 cm³), with a simultaneous integrated boost of 2 Gy to the primary tumor. Three fractions of 2 Gy to the primary tumor were prescribed as a sequential boost, to compensate for the lack of chemotherapy.

Briefly, the KETOCOMP study protocol stipulated the following: (i) consuming a ketogenic diet during the course of RT¹ supplemented with 10 g essential crystalline amino acids (MyAmino, dr.reinwald gmbh+co, Altdorf, Germany); (ii) weekly bodyweight measurements and bioimpedance analysis (BIA) of body composition (seca mBCA 515, seca Deutschland, Hamburg, Germany); (iii) three blood withdrawals; (iv) three quality of life assessments using the EORTC questionnaires [7]. The ketogenic diet was started on the same day that the RT planning CT and baseline measurements were performed. Ketosis was self-monitored daily using urinary ketone test strips and weekly on the days of BIA using finger prick tests (Supplementary Fig. 1).

Initial blood testing 6 days prior to RT revealed low hemoglobin, decreased high-density lipoprotein (HDL) cholesterol, low 25-hydroxy vitamin D, and elevated C-reactive protein (CRP) levels (Supplementary Table 1). During the first week of RT, the patient was admitted to hospital for 2 days to receive erythrocyte transfusions which resulted in subjective improvements in his general condition. During the second week, he reported a slight reduction in the severity of rectal bleeding. The third week marked the beginning of an accelerated body weight and fat-free mass

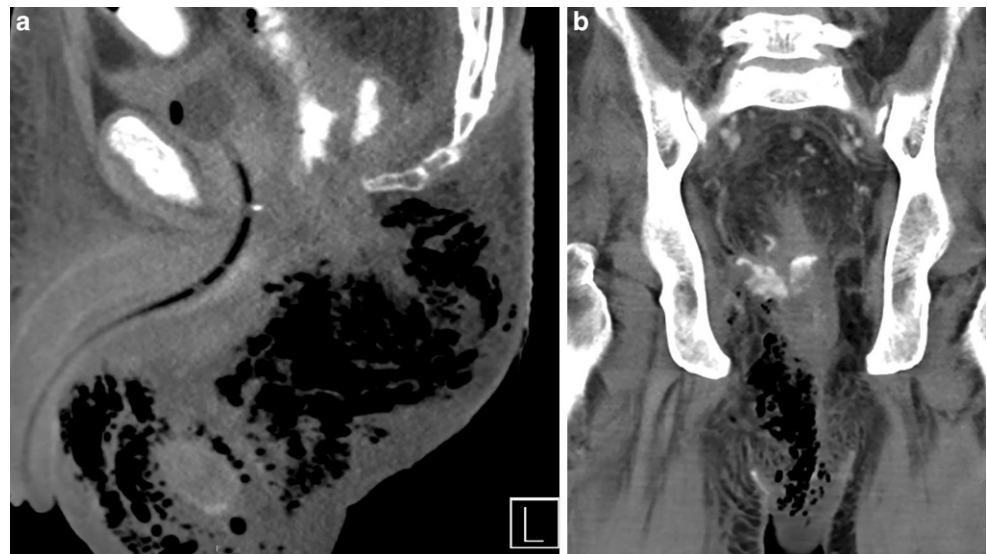
loss (Fig. 1). A 3-day food diary from this week indicated that the patient's diet provided on average 2304 kcal (9660 kJ) per day, which should have been adequate to meet his energy demands. The macronutrient composition of the diet was 101 g of protein (17.5% of energy intake), 198 g of fat (74.8%), and 48.5 g of carbohydrates (9.6%). Therefore—with roughly 1.5 g dietary protein per kg body weight plus an extra 50 g of essential amino acids per week—his protein intake also was judged as adequate, meeting the ESPEN recommendation for cancer patients [8].

The weight loss was thought to originate from a patient-reported increase in stool frequency, with grade 2 diarrhea which also caused him to pause RT for 1 day. According to the patient, these disorders resembled prior episodes of his ulcerative colitis, and he asked for a cortisol prescription that he had used in the past to treat acute episodes of his colitis. The possibility of an RT-induced acute episode of colitis was supported by an increase in CRP levels revealed by the second blood test (Supplementary Table 1). Accordingly, he was prescribed a hydrocortisone suspension (Colifoam, Meda GmbH, Germany) that he started to use during the fourth week of RT as an enema, in addition to oral loperamide.

During the fifth week the patient reported a positive response to cortisol therapy. He also noted a gradual subjective improvement of his knee pain, which was visible objectively as an improved gait and faster walking speed. However, he also reported a newly occurring sharp pain in the perianal region during sitting. This could not be attributed to perianal skin reactions which were rated as mostly grade 1. The pain increased further during the final week of RT, and the patient reported an imperative rectal tenesmus, feeling of pressure in the lower abdomen, and almost complete loss of appetite. A blood test on the final day of RT revealed a marked increase in CRP concentration and further drop of HDL cholesterol (Supplementary Table 1). The tumor marker CEA (carcinoembryonic antigen) measured 0.6 ng/ml, indicating a possible regression of the tumor.

¹ Our version of the ketogenic diet advocates consumption of whole foods with avoidance of industrial and processed foods (except for medium chain triglyceride oil) and anti-nutrients such as gluten. Consumption of animal fats and organ meats as well as plenty of vegetables is recommended.

Fig. 2 Sagittal (a) and coronal (b) contrast-enhanced CT scans showing the gangrene with extensive perianal air inclusions descending into the scrotum



Five days after completion of RT, the patient was transported to the emergency ward of a nearby community hospital. The initial diagnosis was dehydration, somnolence, and an acute attack of ulcerative colitis. Noticeable was a swelling of the scrotum and pressure pain around the symphysis. Leucocyte count was 5100/ μ l, hemoglobin 8.2 g/dl, and CRP 262 mg/l. Within 45 min the patient was transferred to the intensive care unit where infusion, norepinephrine, and antibiotic therapy were started immediately. Within 3 h the patient developed two necrotic areas on the scrotum upon which he was transferred to the urology ward of our hospital with suspected FG. An abdominal contrast-enhanced CT scan revealed circular wall thickening of the rectum and extensive perianal air occlusions reaching from the right buttock into the gluteal muscles and descending into the scrotum (Fig. 2). The primary tumor presented as a cavity connected to the gangrene. In septic shock the patient underwent emergency necrosectomy and ileostomy. Despite maximal postoperative anti-septic therapy, the patient's condition deteriorated further and he soon died of multiple organ failure.

Discussion

This case highlights FG, although extremely rare, as a severe complication of RT for rectal cancer patients. Through his enrollment in the KETOCOMP study, this patient is probably the best-described case of FG development during RT published thus far. In retrospect it appears that several signs of a developing sepsis emerged roughly from the middle of the RT regime:

First, the decline in bioelectrical phase angle (Fig. 1). The phase angle is defined as the arcus tangent of the ratio between whole-body reactance and resistance, and is

influenced by both the water distribution and the integrity of cell membranes. In general, higher values of the phase angle at a specified alternating current frequency are indicative of better cellular health, fat-free mass, and general fitness. Accordingly, low phase angles have been shown to predict mortality in cancer and intensive care unit patients [9, 10].

Second, an accelerated weight and fat-free mass loss starting in the third week of RT (Fig. 1). It is possible that an increased infectious burden resulted in an increased energy demand which the patient was not able to meet through his diet.

Third, the increase in CRP and concurrent drop in HDL cholesterol and IGF-1 concentrations. High CRP and low HDL cholesterol levels are known biomarkers for sepsis, where they display an inverse relationship [11, 12]. HDL particles serve an important anti-inflammatory role by binding and neutralizing bacterial lipopolysaccharide (endotoxin) as well as modulating the inflammatory response of macrophages [13, 14]. The acute-phase response appears to shift HDL function from mainly reverse cholesterol transport towards these anti-inflammatory pathways which may accelerate HDL particle turnover, explaining their drop during sepsis. IGF-1, usually a biomarker of protein intake [15], has anti-inflammatory and anti-oxidative effects too, and low levels have been observed in sepsis [16]. According to Xu et al. [16] excessive release of miRNA-1 through oxidative tissue damage during inflammation may be responsible for the gradual decline of IGF-1 levels with progressing sepsis.

Finally, the occurrence of a sharp pain in the perianal region reported in the fifth week of RT was likely indicative of the spreading gangrene.

Together, these signs point towards the gradual development of FG and sepsis from approximately the end of the

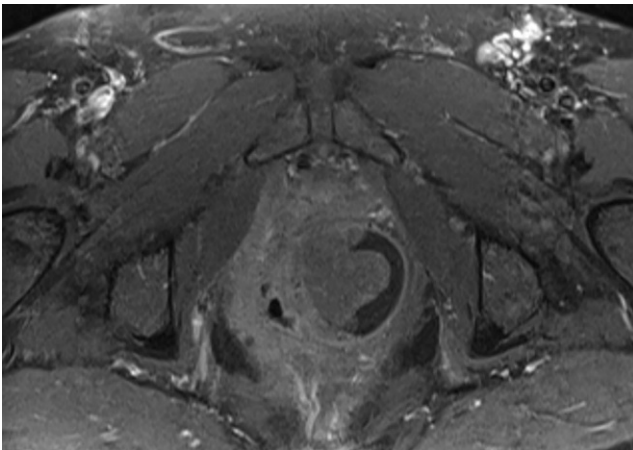


Fig. 3 Pre-treatment axial MRI scan from January 2018. A 3 cm wide pararectal cavity on the right side filled with liquid and air was retrospectively interpreted as a possible origin of the developing gangrene

third week of RT. This is also the timepoint at which the patient started self-administration of hydrocortisone enemas. Nabha et al. [3] implicated chronic steroid enema application as a causative factor in a rectal cancer patient developing FG two years after RT. In addition, our patient had two other major risk factors that could have contributed to the occurrence of FG, namely alcoholic liver cirrhosis and 13.5 pack-years of smoking.

The atypical sequential boost was unlikely the cause of the FG but surely did not improve the situation and should be cautioned against, especially in risk situations such as these. Nonetheless, it was deemed necessary to compensate for the lack of chemotherapy.

It was remarkable that despite the physical deterioration indicated by the biochemical and bioelectrical measurements, the patient's general condition remained fairly stable until the last week of RT, and his self-reported quality of life score was the same at the end of RT than before RT. He was also happy about a marked improvement of his chronic knee arthritis which was obvious by his improved gait and walking speed. These observations are interesting, since they are consistent with anti-inflammatory and analgesic effects of the ketogenic diet [17]. Specifically, recent data have revealed that the ketone body β -hydroxybutyrate suppresses the NOD-like receptor protein 3 (NLRP3) inflammasome [18, 19] that is also involved in several forms of chronic joint arthritis [20]. Scattered radiation received by the knees appears very unlikely as an alternative explanation for the pain reduction, as the cumulative dose was estimated to be <100 mGy. Ketone body metabolism has also been shown to increase tissue tolerance in bacterial infection models by limiting reactive oxygen species induced through anti-bacterial inflammation [21]. While these effects of the ketogenic diet, although possible, remain hypo-

thetical, the patient subjectively described the diet as beneficial for him.

The fulminant development of the gangrene prompted a renewed retrospective analysis of the pre-treatment MRI and diagnostic CT (Fig. 3). Upon careful re-investigation, these not only showed the diagnosed rectal tumor with perirectal infiltration of the fat tissue and lymph node involvement, but also a 3 cm wide pararectal cavity on the right side filled with liquid and air that had been initially diagnosed as a seroma and as unlikely to be associated with the tumor. This may have been the origin of the developing gangrene.

Conclusions

This case highlights the occurrence of FG as an extremely rare but life-threatening complication during neoadjuvant RT for rectal cancer. The combination of alcoholic liver cirrhosis, history of smoking, and steroid enema use appears the most plausible explanation for the development of FG in this patient. The ketogenic diet played no role in the development of the FG; if anything, it may have ameliorated the development and symptoms of the FG. In retrospect, several measurements are consistent with the gradually developing gangrene and bacterial infection, most of which, however, would not have been evaluated outside of our study setting (CRP, HDL cholesterol, IGF-1, and BIA phase angle). Given the rarity of FG and the subsequent unfamiliarity as a complication during RT, our case might help to refresh FG in the awareness of radiation oncologists and radiologist.

Conflict of interest R.J. Klement, G. Schäfer, and R.A. Sweeney declare that they have no competing interests.

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