

Fulminant Fournier's gangrene in a patient with gastric cancer treated with ramucirumab and paclitaxel

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Abstract: Fournier's gangrene (FG) is an uncommon form of necrotizing fasciitis, localized on the external genital organs, perianal region, and abdominal wall, accompanied by thrombosis of the feeding arteries, leading to gangrene of the skin and subcutaneous tissue, with manifestations of rapid clinical progression and multiple organ failure. Ramucirumab is a recombinant human immunoglobulin G1 monoclonal antibody that binds to the extracellular binding domain of vascular endothelial growth factor receptor-2 (VEGFR-2) and prevents the binding of all VEGFR ligands. The literature describes bevacizumab, aflibercept, and regorafenib associated with FG in patients with colorectal cancer. According to our knowledge this is the first report of FG possibly related to ramucirumab in a patient with gastric cancer. If not recognized in time, it can lead to fatal complications.

Keywords: Fournier's gangrene, gastric cancer, paclitaxel, ramucirumab

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Introduction

Fournier's gangrene (FG) is an uncommon disease of the genitals, found almost exclusively in men. It is a specific form of necrotizing fasciitis, localized on the external genital organs, the perianal region, as well as in the abdominal wall, accompanied by thrombosis of the feeding arteries, leading to gangrene of the skin and subcutaneous tissue, with manifestations of severe intoxication, rapid clinical progression, and multiple organ failure.¹ Several predisposing factors are described, such as diabetes, obesity, and malignant disease, often accompanied with immunocompromised status resulting in high mortality rates. Four agents that target angiogenic pathways (i.e. bevacizumab, ramucirumab, aflibercept, and regorafenib) in combination with standard chemotherapy are approved for metastatic colorectal cancer. Ramucirumab is the preferred agent in combination with paclitaxel for the treatment of unresectable, locally advanced, recurrent or metastatic gastric cancer. In contrast to other agents, ramucirumab is a recombinant human immunoglobulin G1 monoclonal antibody that binds to the extracellular binding

domain of VEGFR-2 and prevents the binding of all VEGFR ligands: VEGF-A, VEGF-C, and VEGF-D. Through blocking activation of VEGFR-2 by VEGF-A and the other VEGF ligands, ramucirumab inhibits the angiogenesis pathways involved in the development and progression of gastric cancer.² Anti-angiogenic drugs, such as bevacizumab, aflibercept, and regorafenib, have already been described to have a possible connection with FG in patients with colorectal cancer. According to our knowledge this is the first case of FG reported in patients with gastric cancer and in patients treated with ramucirumab.

Case presentation

A 76-year-old man with gastric cancer was surgically treated in June 2017 (gastrectomy, omentectomy, splenectomy, and subtotal pancreatic resection, esophagojejunostomy, and entero-enteral anastomosis Roux); pathohistology findings confirmed gastric adenocarcinoma, pT4N2bM0, Her-2 negative. He received five cycles of adjuvant chemotherapy with cisplatin

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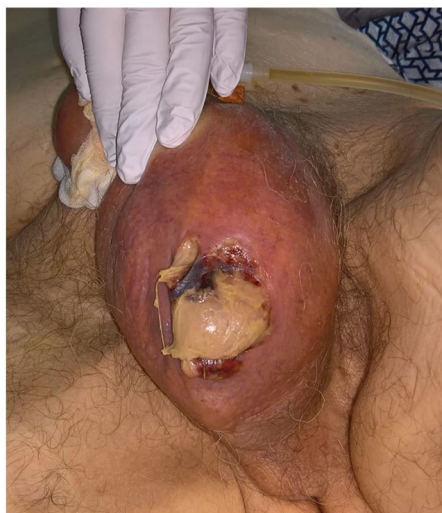


Figure 1. Scrotal perforation in a patient with necrotizing fasciitis.

and 5-fluorouracil from July 2017 to October 2017. The planned sixth cycle of chemotherapy was refused by the patient. He was in follow up until August 2018 when magnetic resonance imaging confirmed liver metastases and ascites, general condition ECOG 0.

In September 2018 he started first-line chemotherapy for metastatic gastric cancer with ramucirumab 8 mg/kg on day 1 and day 15, and paclitaxel 80 mg/m² on day 1, day 8, and day 15 every 4 weeks. During hospitalization for the second cycle of chemotherapy, the patient had mild upper abdominal pain, fatigue, suprapubic discomfort, and generalized edema including face, arms, legs, and scrotum. He had no fever and no other major changes in his condition. Laboratory findings showed insignificant decreases in potassium and calcium levels, serum albumin was 24.8 g/L (range 35.0–52.0 g/L), leukocytes $12.1 \times 10^9/L$ (range $3.4\text{--}9.7 \times 10^9/L$), hemoglobin 105 g/L (range 139–175 g/L), and C-reactive protein (CRP) 84 mg/L (normal <5 mg/L). After the appearance of scrotal and penile edema associated with leukocytosis and CRP elevation, and oliguria, a urinary catheter was inserted. Computed tomography (CT) scan showed stable hepatic and lymph node metastases and ascites. A urologist was consulted because of signs of scrotal inflammation and antimicrobial therapy was started. After 2 days, the left scrotal sac perforated with abundant

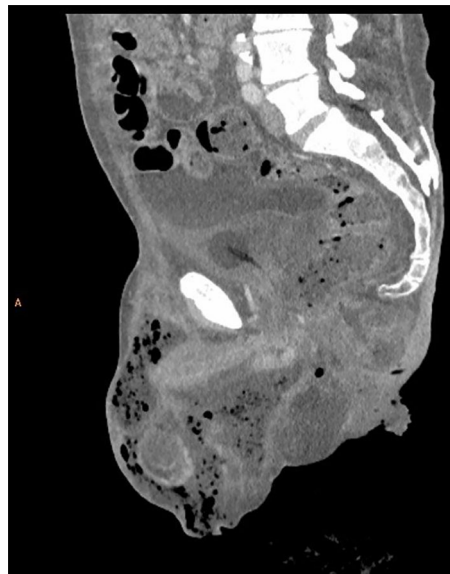


Figure 2. Sagittal CT scan with bubble gas appearance in the scrotum and perirectal and presacral space with fat tissue inflammation. CT, computed tomography.

purulent drainage and suspected leakage of testicular tissue (Figure 1). Ultrasound and pelvic and scrotal CT scan showed extensive inflammation, multiple and confluent abscesses of pelvic and perirectal fat tissue, involving the ischioanal fossa, perineum, suprapubic fat tissue, and scrotum. There was no sign of intestinal herniation (Figure 2).

With the diagnosis of FG, the patient was taken for an urgent operation, which included drainage of purulent secretion from the scrotum, bilateral orchiectomy, circular incision around the penile glans, and removal of penile skin. The histology report described large areas of necrotic skin, however, the testicles were intact. Blood and tissue cultures were collected and broad-spectrum antibiotic treatment was initiated; *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis* were isolated. In the following days he underwent two additional excisional debridements and thereafter autologous split-thickness skin graft for penile coverage. These two additional interventions were complicated by postoperative hemorrhage. The patient died about 7 weeks after the diagnosis of FG and a prolonged treatment with antibiotics, parenteral nutrition, analgesics, and intensive supportive care.

Discussion

FG in oncological patients has been described as being related to tumor location (e.g. rectal/sigmoid cancer), factors which increase the risk of infection in the area of impaired microvascularization (e.g. immunosuppression, diabetes), or adverse events of anti-angiogenic therapy that lead to blood supply disorder. Known risk factors for FG are diabetes mellitus type 2, i.v. drug use, obesity, malignant disease, immunosuppression, recent surgery, and trauma. Rare cases where the occurrence of this complication is unrelated to any known cause are classified as idiopathic. Treatment consists of an urgent surgical procedure of necrectomy, application of antimicrobial therapy, and other measures of supportive treatment, and plastic-reconstructive surgery. Despite the long and complex treatment, mortality is still high.

In this case, the patient was in very good overall condition without comorbidities. He did not take any medication, smoke, or consume alcohol, and did not report any trauma. Risk factors in our patient included immunosuppression related to chemotherapy and treatment with the anti-angiogenic drug ramucirumab.

Ramucirumab can cause arterial thrombosis which could have triggered the necrotizing fasciitis. Thereafter, necrotizing fasciitis rapidly develops without systemic clinical signs of inflammation or significantly changed laboratory parameters, possibly due to the age and general energy of the patient. Also, fever, which is typical for this condition, was notably absent.³ Although artery thrombosis is a pathognomonic sign of FG, the tissue has not been analyzed histologically due to the extent of the necrosis.

The testicular tissue is not typically affected due to the different blood supply of the tissue contrary to the scrotum and perineum.⁴ The testicular artery is a branch of the abdominal aorta that supplies blood to the testis. The scrotum is supplied from the arteries that arise from the internal iliac artery, external iliac artery, and femoral artery. In our case, despite the extensive skin and subcutaneous tissue necrosis, the testes were not affected, which is an indirect sign of blood supply disturbance.

The mechanism of action of anti-angiogenic drugs is inhibition of VEGF signaling by blocking

the VEGF ligand or VEGF receptor function and altering tissue and tumor vascularization. Arterial thrombotic events are well-described side effects of anti-angiogenic therapy. In addition a patient with VEGF inhibitor therapy has an increased tendency for bleeding and prolonged wound healing, which can further complicate postoperative recovery.

Cases of FG described in the literature were associated with colorectal cancer and the use of anti-angiogenic drugs like bevacizumab,⁵⁻⁸ aflibercept,⁹ and regorafenib.¹⁰ Mechanisms of FG included subcutaneous artery thrombosis and tissue ischemia.

There is no reported causal relationship of paclitaxel and FG in the literature. The use of chemotherapy may mask the clinical picture with the lack of an inflammatory response.

The exact mechanism of the onset of FG by the action of VEGF inhibitors has not been elucidated, although the occurrence of necrotizing fasciitis has been officially reported as a possible rare complication in patients with cancer during bevacizumab administration.⁶ In the affected area, VEGF inhibitors impede anti-inflammatory response by acting on blood vessels, reducing neoangiogenesis and impairing healing. Also, the thrombogenic effect leads to ischemic injuries that further support the progression of necrosis. Therefore, it is necessary to keep in mind the possibility of this complication while administering VEGF inhibitors, due to early diagnosis and early initiation of treatment. Further investigations into the mechanism of FG are certainly needed.

This case presented with rapid, fulminant progression of FG and lack of clinical signs and symptoms as well as no major changes in laboratory parameters. We described the case of FG in a patient with gastric cancer with atypical onset of disease complications possibly related to ramucirumab treatment. It is important to consider this complication in patients treated with anti-angiogenics because of high mortality and morbidity, and the need for urgent surgical procedure.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Informed consent

Written informed consent for patient information and images to be published was provided by the patient.

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