

Fatal Necrotizing Fasciitis after Intramuscular Fulvestrant

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Abstract

Necrotizing fasciitis is a life-threatening infection with necrosis of the fascia and the subcutaneous tissues that usually progressed rapidly to a septic shock hence causing high rates of mortality. Risk factors include diabetes, peripheral vascular disease (PVD), immune compromise or recent surgery. Although there are published some cases of necrotizing fasciitis after intramuscular injections, mostly with nonsteroidal anti-inflammatory drugs (NSAIDs), this entity is rare. Hence we report the first case of a 55-year-old woman with metastatic breast cancer presenting to our hospital with a necrotizing fasciitis of the gluteus after intramuscular injection of Fulvestrant (an estrogen receptor antagonist for the treatment of hormone receptor-positive metastatic breast cancer patients).

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Case Report

A 55-year-old woman was admitted in the emergency room with nausea, diarrhea (20 times within 24 hours), abdominal pain and weakness but she had no signs of dehydration, fever or confusion.

The patient had a history of hypertension, allergy to Penicillin and her oncologic medical record showed that she had a stage I invasive lobular breast carcinoma diagnosed in 1994 treated with right breast lumpectomy and axillary nodes dissection followed by adjuvant radiotherapy of the breast and Tamoxifen for 5 years.

In 2003 she went into a right mastectomy because of a local relapse of the invasive lobular breast cancer. The immunohistochemical profile shows edestrogen receptor/progesterone receptor (ER/PR) positive, human epidermal growth factor receptor 2 (HER2) negative and Ki67 negative. After the surgery adjuvant Tamoxifen and Goserelin was prescribed for another 5 years.

In 2013 she developed multiple bone metastasis localized in lumbar spinal column, ribs, sternum and pelvis bone. She was treated with non-steroidal Aromatase Inhibitor Letrozole 2.5 mg/day for two years with stable metastatic disease.

In June 2015 she had a bone progression disease and she started second hormonal therapy with intramuscular Fulvestrant at the loading dose of 500 mg days 1, 14 and 28 and every 28 days thereafter. The last intramuscular Fulvestrant dose was administered at her primary care center 48 hours before she felt sick. She complained the last injection was a little more painful than the previous one.

On admission her blood pressure was 100/60 mmHg, her pulse was 68 beats/min and the temperature was normal. The abdominal examination revealed a mild tenderness without signs of peritoneum irritation. Laboratory analysis showed a normal leukocyte count, normal platelet count and normal coagulation. Electrolytes and creatinine levels were also normal. However the hematocrit and hemoglobin level were low (26.9% and 9.1 g/dL respectively), high C-reactive protein of 109 mg/L (normal range, 0-10) and the blood gas analysis revealed metabolic acidosis (pH 7.31; bicarbonate 19.1 mmol/L).

In a few hours her clinical status deteriorated rapidly and she suffered a septic shock with severe metabolic acidosis, pancytopenia and impaired coagulation. Her abdominal pain got worse and she developed hypoesthesia in the right leg. The body computerized tomography (CT) scan showed an extensive necrotizing fasciitis affecting the rectum wall (Figure 1), right gluteus,



deep and superficial pelvic muscles (Figure 2) or mesenteric fat (Figure 3) among others. She started primary aggressive resuscitation with empiric intravenous antimicrobial treatment with Meropenem and Vancomycin, intravenous fluids and other intensive supportive measures (like Noradrenaline and Prothrombin Complex Concentrate) and then she was taken for surgery immediately. The intraoperative exploration showed erythema and edema in the right gluteus with hemorrhagic blisters and necrosis of skin (Figure 4) and soft tissue emphysema (crepitus in the overlying skin). A laparotomy was performed showing hemorrhagic malodorous peritoneal fluid without enteric wastes, signs of bowel ischemia, gas in epyplon and mesenteric fat and emphysema in the whole pelvis surrounding rectum. Surgical extensive drainage and debridement comprising the perianal region and especially in the right gluteus were done, necrotic tissue of the right gluteus was removed, washing of the peritoneal cavity and a lateral colostomy was required. In the peritoneal fluid culture a *Clostridium* sp was isolated. Despite of intensive care and surgery the patient died 3 hours after surgery of multiorgan failure

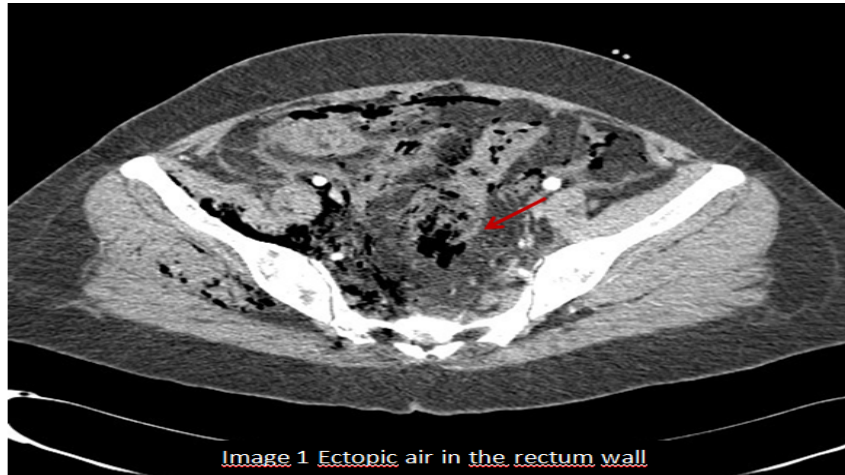


Figure 1: Ectopic air in the rectum wall

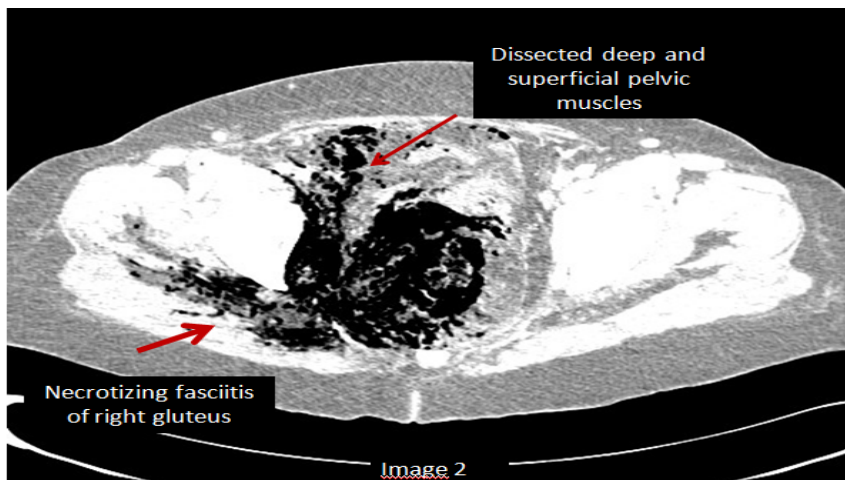


Figure 2: right gluteus, deep and superficial pelvic muscles.

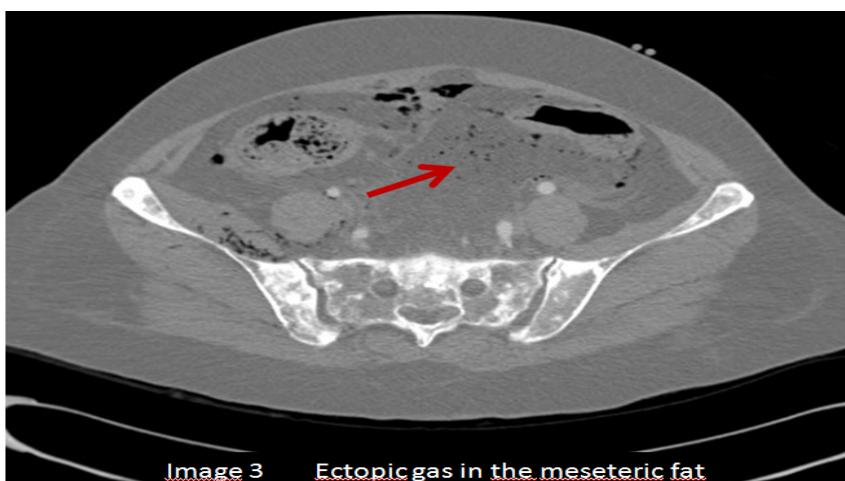


Figure 3: Ectopic gas in the Mesenteric fat.



Figure 4: Erythema and blisters in the right gluteus.

Discussion

Necrotizing fasciitis (NF) is a group of rare life-threatening infection of the skin, muscles and soft tissues with necrosis of the fascia and the subcutaneous tissues^[1]. NF usually progressed rapidly causing massive tissue destruction, septic shock and high rates of mortality (almost 100% without treatment)^[2]. Commonly the NF can develop in the extremities, the perianal region, the abdominal wall or the genital area (called Fournier's Gangrene)^[3,4a]. According to bacteriologic findings there are four types of NF: type I (polymicrobial infection), type II (streptococcus a infection), Type III (Clostridium infection) and Type IV (fungal infections). The most frequent risk factors associate to NF is diabetes, peripheral vascular disease (PVD), immunodeficiency, hypertension, recent surgery or local trauma. Minor local traumas like burns, insect bites or intramuscular injections have been reported as causes of NF or Fournier's Gangrene^[2].

There are some cases published of NF after intramuscular administration of medicines particularly nonsteroidal anti-inflammatory drugs (NSAIDs) Orlando A et al^[4b] reported a case of fatal NF in a woman given a NSAID after an endoscopic procedure. The hypothesis that was made is that the endoscopic procedure caused bacteraemia and NF was favored by the intramuscular NSAIDs injections. In fact, in immunosuppressed patient such as the one described in this report, could occur a bacteraemia that may predispose to fasciitis after an intramuscular injection. This independently of the drugs administered^[4-9].

The NSAIDs per se have been related to NF streptococcal infection independently of the way of administrative though this association is not completely clear. But without question intramuscular administration can cause tissue necrosis, infection on the local injection and subsequently spread the infection to the soft tissues causing NF and this rare complication may be independent of the drug given^[2].

Patients with NF after intramuscular injections can present with mild initial symptoms like local pain, itching, erythema or edema in the affected area. As the infection spreads local signs like skin necrosis, hemorrhagic blisters or crepitation in the overlying skin can be found and systemic toxicity like symptoms of septic shock.

In our patient local pain was an initial unspecific symptom after the intramuscular injection of Fulvestrant. When she was admitted general symptoms were predominant with a fulminant evolution to a septic shock as the examination and laboratory findings demonstrated (systemic acidosis, pancytopenia or coagulopathy)^[2-4]. As the radiologic images show the spread of the infection was massive affecting the rectum wall (Figure 1), right gluteus, deep and superficial pelvic muscles (Figure 2) or mesenteric fat (Figure 3) with gas formation in all of this location indicating anaerobic infection such Clostridium species. Local surgical findings were also typical and remarkable of NF with signs of skin necrosis and gas formation everywhere. The administered treatment with broad spectrum antibiotics and extensive surgical debridement is the recommended for NF but in our case was not enough because of the severity of the clinical symptoms.

Looking for the etiology or risk factors of NF in our particular case she had a metastatic breast cancer just localized in bones but this situation can be consider an immunosuppression environment which increases the risk of infection. She had a medical history of hypertension and although this was not a typical risk factor in a recent review was included as a co-morbidity found in patients with NF. Obviously the minor trauma of the intramuscular injection was the portal of entry for the infection but could the type of drug, Fulvestrant, may increase the risk of NF?

Fulvestrant^[10] is an estrogen receptor antagonist indicated for the treatment of postmenopausal women with estrogen positive, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant anti-estrogen therapy or disease progression on therapy with an anti-estrogen. After the Phase III trial CONFIRM the recommended dose of Fulvestrant is intramuscular 500 mg (2 injections of 250 mg) day 1, 14, 28 and every 28 days thereafter as our patient received. The solution of the injection is viscous (contains castor oil, ethanol, benzyl alcohol and benzyl benzoate as excipients) that is why Fulvestrant should be administered slowly (1-2 minutes/injection) as two consecutive intramuscular injections one in each buttock by healthcare professionals only to avoid local site reaction. Fulvestrant is a well-tolerated treatment with well-known common side effects related to the hormone

imbalance (hot flushes, joint disorders, urinary tract infections, headache or gastrointestinal disturbances) or to the way of administration (mild injection site reactions like pain, erythema or haematoma)^[11]. Our clinical case is the first case reported of a local severe complication after an intramuscular injection of Fulvestrant. However local reactions including myositis at the injection site were seen in animal species both with to the control arm (saline intramuscular injection) and the Fulvestrant arm but severity of myositis in rabbits were higher with Fulvestrant hypothesizing that the combination of intramuscular injection with Fulvestrant may increase the risk of severe complications^[11].

Fulvestrant is a very active drug for metastatic breast cancer patients with a good toxicity profile which make the drug a very good option for patients with hormone-responsive advanced breast cancer. The drug is currently prescribed in thousands of women worldwide and its use presumably will increase owing to new indication in combination with Palbociclib according to PALOMA-3 results^[12].

Therefore Fulvestrant should be administered for trained health care professionals following the instructions of administrations and the preventive aseptic measures^[13].

Conclusions

This is the first case reported of a fatal necrotizing fasciitis after intramuscular Fulvestrant in a metastatic breast cancer patient. NF is a rare life-threatening infection which requires an early diagnosis to establish a rapid therapy based on antibiotic therapy and extensive surgical debridement. NF after an intramuscular injection is an uncommon complication but with the extensive use of Fulvestrant we should be aware of what could happen.

Conflicts of Interest: There is no conflicts of interest.

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