

Necrotizing Fasciitis as Complication use of Bevacizumab with Chemotherapy

Cantürk emir, Can Aktas, Alp Giray AYDIN

Department of Emergency Medicine, Koc University Hospital, İstanbul, Turkey

Necrotizing fasciitis is an uncommon, severe, life-threatening soft tissue infection involving the subcutaneous tissue. Immunocompromised and diabetic patients are at a higher risk of developing necrotizing fasciitis. One of the pathophysiologic mechanism of necrotizing fasciitis is subcutaneous arteries thrombosis and tissue ischemia. Bevacizumab, one of the agents used in cancer treatment, blocks the activity of vascular endothelial growth factor (VEGF) receptor. In recent years, it is used in combination with paclitaxel and carboplatin due to increase survival rate. The frequent use of this combination caused patients to apply to the emergency department with some side effects. Necrotizing fasciitis is one of the rare side effects of this combination. Here, we present a patient with ovarian cancer who was admitted to the emergency department with severe leg pain, whose initial examination and tests were normal, and then NF developed within hours and then arrested.

Keywords: Fasciitis, Necrotizing, Drug Therapy, Bevacizumab, Emergencies

Short Title in English: Fatal chemotherapy complication: Necrotizan Fasciitis

Introduction

Cancer is one of the most common and fatal diseases in modern era. Current treatment options are traditional chemotherapeutic agents, antiangiogenic therapy and immunotherapy. Antiangiogenic agents are important in the treatment of many solid tumors. Vascular endothelial growth factor (VEGF) is an important target for therapy as it is the primary mediator in angiogenesis and induced by multiple stimuli in tumor development (1). Bevacizumab, one of the antiangiogenic agents (2, 3), shows a significant success rate in the treatment of non-small cell lung cancer as well as colorectal, gastric and ovarian cancer (4). In recent years, it is used in combination with paclitaxel and carboplatin due to the increased non-progressive survival rate in long term. It's more widely used as a result of these promising research but emergency admissions are also increasing due to the various side effects. Necrotizing fasciitis (NF) is reported in a few cases as one of the side effect of bevacizumab treatment. Traditional chemotherapeutic agents can also cause several side effects and there are cases of necrotizing fasciitis reported after the combination treatment of bevacizumab and paclitaxel (5, 6).

Here, we report a patient with necrotizing fasciitis as a result of combination treatment of bevacizumab, carboplatin and paclitaxel in a patient with ovarian cancer, admitted to the emergency department (ED).

Case Report

65-year-old female patient came to ED with pain on the outer side of her left leg and cramps on the left foot dorsum. She described severity of her pain as 10/10. Her medical history includes hypertension, ovarian cancer diagnosed 2 months ago with liver metastases and rectum invasion. Her surgical history includes cholecystectomy, splenectomy, total abdominal salpingoophorectomy, omentectomy and appendectomy. After surgery, she was started on bevacizumab, paclitaxel, carboplatin combination therapy. She took her second dose of treatment 10 days ago. Lower extremity physical examination findings were completely normal. Homans test was negative, extremities were warm, and pulses were equal bilaterally. Lower extremity color doppler USG was ordered. Blood flow was evaluated as normal. No deep vein thrombosis and no superficial venous thrombophlebitis were found. In superficial ultrasound exam to left lateral cruris, no pathologies were detected in cutaneous and subcutaneous tissues. Blood tests were unremarkable. As analgesic treatment, the patient was given paracetamol 10 mg/ml IV, dexketoprofen 50 mg IV, tramadol hcl 100 mg IV in ED. After treatment, her pain diminished and since no pathologies were detected and she was discharged.

After 4 hours of her discharge, she came to ED with pain, ecchymosis and edema in her left leg. She was agitated. Blood pressure: 90/60 mmHg, respiratory rate: 16/min, pulse: 98/min, SpO₂: 99%. In lower extremity examination, her lower 1/3 thigh and lower leg was ecchymotic, edematous and there was subcutaneous crepitation to palpation. Femoral pulses were present, distal pulses were weak and palpable. 2-view radiographs of cruris were ordered; there were subcutaneous air densities lateral to knee joint soft tissue and on fibula (Figure 1). Lower extremity Doppler ultrasound was performed. subcutaneous fat tissue increased, there was 6

mm effusion between fat tissue and fascia, with comet artifacts. Left lower extremity CT was performed. Air densities on femoral vein, saphena magna; on vascular traces through popliteal fossa, cruris and foot; on distal leg, knee and cruris level were commented as necrotizing fasciitis (Figure 2,3). Infectious diseases and orthopedics were consulted. Meropenem 1 gr IV, metronidazole 500 mg IV was given in ED. While planning the patient's hospitalization, the patient was suddenly arrested in the emergency department and CPR was performed but the patient was unresponsive.

Discussion

Necrotizing fasciitis most frequently involves the abdominal wall, peritoneal membranes and lower extremities. NF cases were reported as more likely to arise in the presence of HIV infection, diabetes, cancer, alcoholism, vascular insufficiencies, organ transplant related immunodeficiencies and chronic diseases (7). Use of bevacizumab and paclitaxel were reported as one of the causes of NF. In 2013 during a safety research conducted for bevacizumab therapy, 52 NF cases and 17 related deaths were reported from November 1997 to September 2012 (8). NF has been recorded as one of the side effects since 2013. World Health Organization reported 7 NF cases developed after pactikaxel use as a combination therapy with bevacizumab (9) The case we presented supports the literature that bevazicumab and paclitaxel combination therapy increases the risk of developing necrotizing fasciitis. Although the mechanism is not clear, progression rate of necrotizing fasciitis can last days from its beginning or develop quickly in hours ending up with death. In our case, the disease showed a rapid course and resulted in death within a few hours.

Conclusion

Although it is a rare complication, physicians should be reminded of the fact that patients admitted to ED with acute extremity pain and who are taking combined bevacizumab and paclitaxel therapy, carry a risk of having NF with a rapid progression and death.

References:

1. Vokes E, Herbst R, Sandler A. Angiogenesis inhibition in the treatment of lung cancer. Clin Adv Hematol Oncol. 2006; 4 (23):1-10. quiz 11-2.
2. Fujiwara K, Monk BJ, Lhommé C, et al. Health-related quality of life in women with recurrent ovarian cancer receiving paclitaxel plus trebananib or placebo (TRINOVA-1). Ann Oncol 2016; 27(6): 1006-1013. doi: 10.1093/annonc/mdw147.
3. Klag N, Walter AC, Sheely KM, Manahan KJ, Geisler JP. Is the routine use of bevacizumab in the treatment of women with advanced or recurrent cancer of the cervix sustainable? Clinicoecon Outcomes Res. 2016; 8: 287-291. doi: 10.2147/CEOR.S71
4. Cong J, Liu R, Hou J, Wang X, Jiang H, Wang J. Therapeutic effect of bevacizumab combined with paclitaxel and carboplatin on recurrent ovarian cancer. J BUON 2019; 24(3): 1003-1008.

5. Bilton BD, Zibari GB, McMillan RW, Aultman DF, Dunn G, McDonald JC. Aggressive surgical management of necrotising fasciitis serves to decrease mortality: a retrospective study, *Am Surg*; 1998; 64: 397-400. discussion 400-1.
6. Akbaş T, Bilgin H, Aykut U, Karakurt S. Nekrotizan fasiit: gecikmiş cerrahi müdahale mortaliteyi artırır. *Düzce Üniversitesi Sağlık Bilimleri Enstitüsü Dergisi*. 2015; 5(3): 84-88.
7. Modlinska A, Osowicka M, Buss T., Niemierko ML. The craniofacial necrotizing fasciitis after a minor trauma in an elderly white woman. *J Clin Exp Dent* 2014; 6(3): 307-309. doi: 10.4317/jced.51368.
8. Wong J. Bevacizumab is linked to cases of necrotising fasciitis. *Lancet Oncol*. 2013; 14: 259. doi:[https://doi.org/10.1016/S1470-2045\(13\)70222-5](https://doi.org/10.1016/S1470-2045(13)70222-5).
9. Amer NM, Niaz R. Necrotizing fasciitis as a complication of taxanes: a case report. *J Cancer Metastasis* 2018; 4: 34. doi: 10.20517/2394-4722.2018.09.

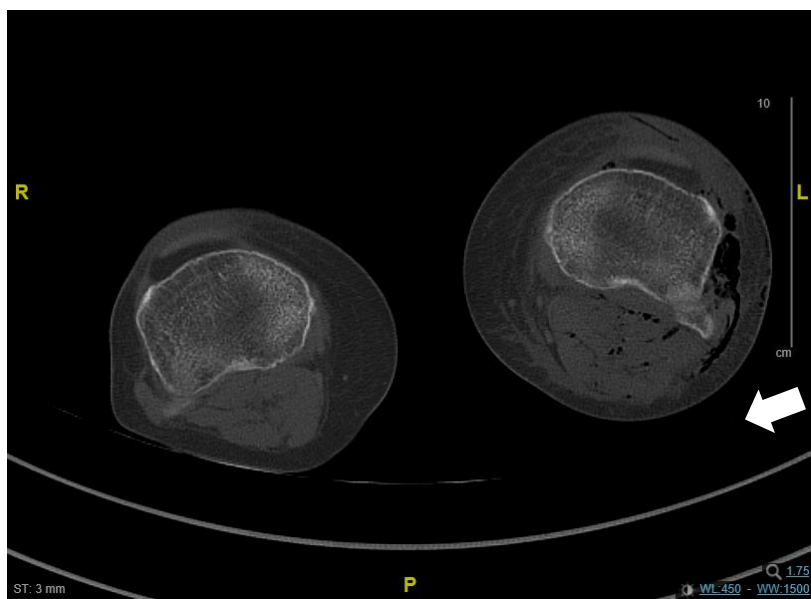
Figure1. Left Knee X-ray. Subcutaneous air densities in the superposed area over the soft tissues and fibula, adjacent to the lateral side of the knee joint



Figure 2. Lower extremity CT. Air densities at the knee and cruris levels



Figure 3.Lower extremity CT



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