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CASE REPORT

Panitumumab Induced Forearm Panniculitis in Two Women With Metastatic Colon Cancer

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Abstract: ***Background*:** Panitumumab is an EGFR inhibitor used for the treatment of metastatic colorectal cancer (mCRC), even if its use is related to skin toxicity.

***Case Presentation*:** We report the development of forearm panniculitis in two women during the treatment with Panitumumab (6 mg/Kg intravenous every 2 weeks) + FOLFOX-6 (leucovorin, 5-fluorouracil, and oxaliplatin at higher dosage) for the treatment of mCRC.

***Results*:** In both patients, clinical, laboratory and radiological evaluation documented the presence of a local panniculitis, probably related to panitumumab (Naranjo score: 6). Panatimumab discontinuation and antimicrobial + corticosteroid treatment induced a remission of skin manifestations.

***Conclusion*:** We reported for the first time the development of panniculitis during Panitumumab treatment, and we documented that the treatment with beta-lactams to either fluoroquinolones or oxazolidinone in the presence of corticosteroid improves clinical symptoms in young patients with mCRC, without the development of adverse drug reactions or drug-drug interactions.

Keywords: Panitumumab, panniculitis, adverse drug reaction, EGFR, mCRC, FOLFOX.

1. INTRODUCTION

Dermatologic toxicities represent a relevant problem during each drug treatment and it significantly impact the patients' quality of life (QoL), reducing compliance and clinical outcomes [1-3].

Skin toxicities are commonly described during the treatment with the epidermal growth factor receptor (EGFR) inhibitors. Panitumumab is an EGFR inhibitor used for treatment of metastatic colorectal cancer (mCRC).

In particular, the administration of Panitumumab to FOLFOX (leucovorin 200 mg/m² IV infusion, 5-fluorouracil 600 mg/m² IV infusion and oxaliplatin 85 mg/m² IV infusion) or FOLFOX4 (FOLFOX + 5-fluorouracil 400 mg/m² bolus), or FOLFOX6 (FOLFOX4 at higher dosage) as first-line treatment for both RAS (rat sarcoma viral oncogene homolog) wild-type or KRAS (Kirsten rat sarcoma viral oncogene homolog) mCRC significantly improved overall survival compared to FOLFOX alone [4] and to FOLFOX plus bevacizumab [5]. Unfortunately, the development of skin rash, papules and pustules in the face, scalp, and trunk, typically with or without pain have been described within the first 3 weeks of treatment with EGFR inhibitors [6-8], although these adverse drug reactions could be an indicator of a biological effect [8]. Herein, we report two patients that developed severe panniculitis during panitumumab treatment successfully treated with empirical antibiotic therapy + corticosteroid.

2. CASE REPORTS

2.1. Case 1

A 44-year-old woman, with a clinical history of descending colon cancer (stage IV) with liver and peritoneal metastases, received an anticancer treatment with FOLFOX-6 + Panitumumab (standard dosage: 6 mg/Kg intravenous every 2 weeks) from April 2017 up to November 2017 and then with 5-Fluorouracil + Panitumumab until May 2018.

In May 2018, the patient presented fever (39°C) and severe inflammation on left forearm (Fig. **1**). Clinical evaluation revealed the presence of edema, rubor and sever pain (VAS score 8/10) on left forearm, while laboratory test

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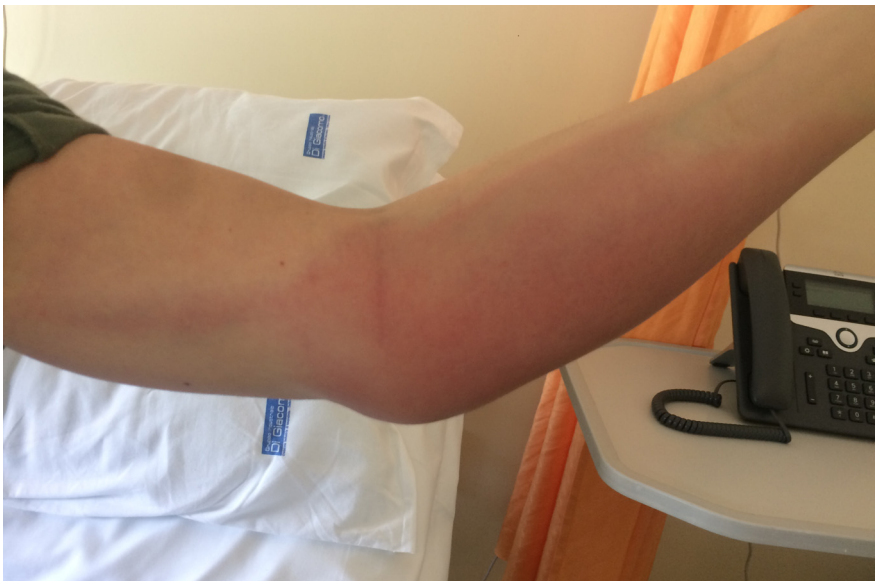

Fig. (1). Panniculitis in the first woman at the admission. It is possible to see the presence of a large area of erythema and lymphangitis.

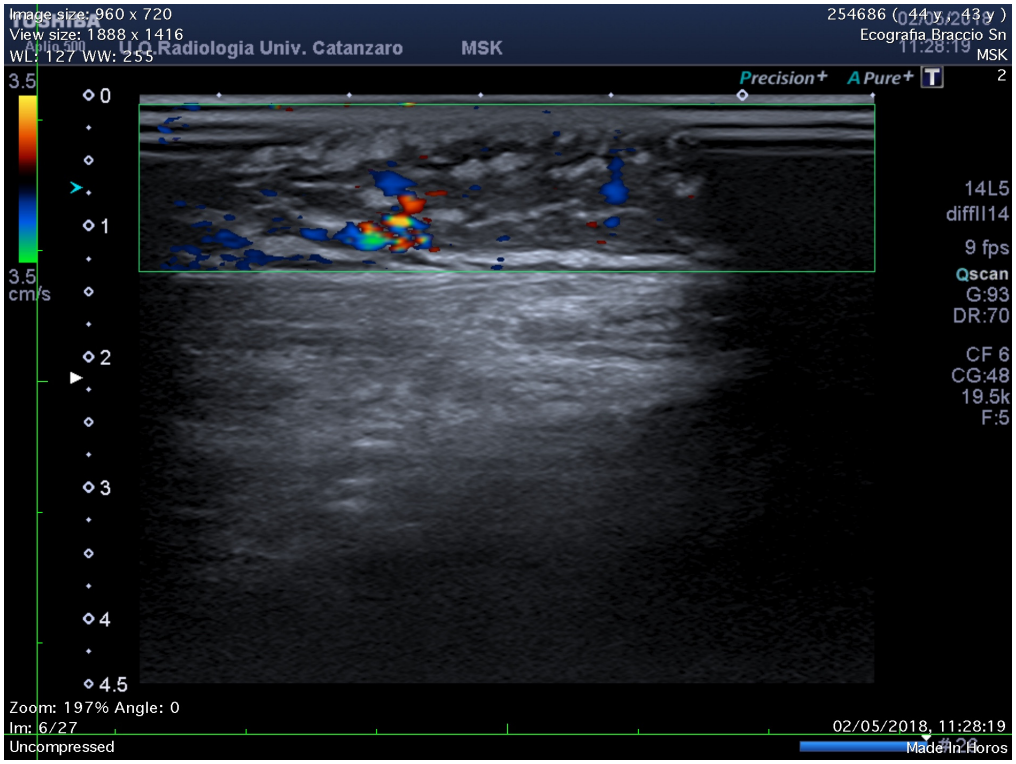

Fig. (2). Ultrasound of the forearm: it is possible to note inhomogeneity of the sub-cutis with tissue edema and marked structural disruption of the subcutaneous adipose panniculus.

showed a significant increase in both neutrophil cells count (25,500 cell/mmc; normal range 2,500-7,700) and procalcitonin (PCT 5.79 ng/ml; normal range < 0.5 ng/mL), while blood culture failed to detect infections in the bloodstream. Forearm ultrasound documented an area with blurred margins of thickening and with marked structural disruption of the subcutaneous adipose panniculus confirmed by Magnetic Resonance Imaging (MRI), that also showed an edema of both subcutaneous adipose matrix and fibrous septa on the whole forearm on the ulnar side without involvement of the underlying muscle (Figs. **2** and **3**). A diagnosis of panniculitis was postulated and Naranjo probability scale, [9] documented a possible association between Panitumumab and panniculitis (score 6).

Panitumumab was dismissed and an empirical antibiotic treatment with Linezolid (600 mg bid) and Ceftriaxone (1 gr bid) plus a corticosteroid (betamethasone, 2 mg bid) was started with an improvement of clinical symptoms in 3 days (fever 36.5°C, PCT <0.5 ng/mL). Betamethasone was dismissed and about 3 days later a new clinical and laboratory evaluation documented a neutrophilic leukocytosis (16,000

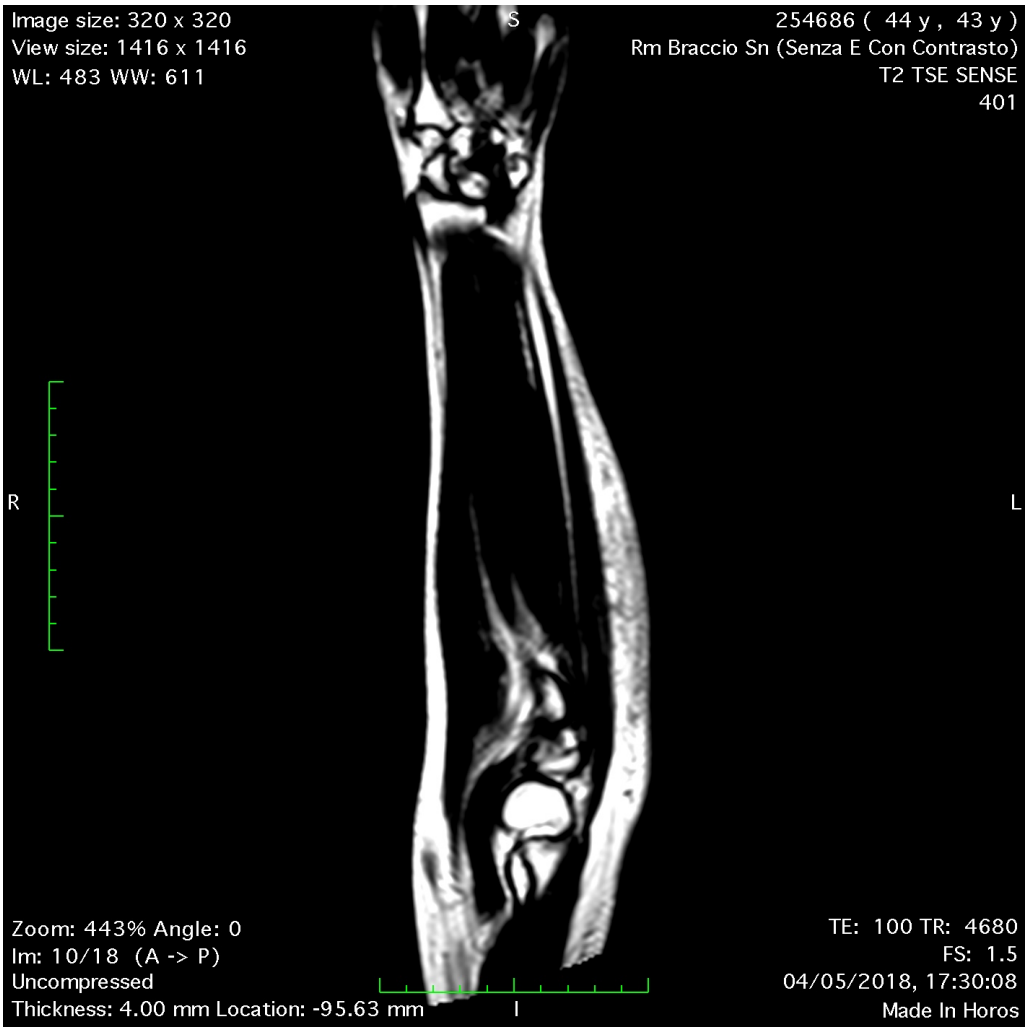

Fig. (3). Magnetic resonance: thickened of sub-cutis and structural disruption of the subcutaneous adipose panniculus.

cell/mmc), therefore ceftriaxone was discontinued, meropenem (2 gr tid) was started for 10 days and then linezolid was changed to tedizolid (200 mg/day) with a complete remission of both clinical symptoms and radiological signs in about 2 months and without the development of adverse drug reactions or drug-drug interactions.

About 1 month later, Panitumumab was added again in the treatment and a new follow-up on January 2019 did not show any further adverse drug reactions.

2.2. Case 2

A 49-year-old woman, with a clinical history of descending colon cancer (stage IV) with liver metastases, on April 2018 started a treatment with FOLFOX-6 + P and 1 month later (after the second administration of P) she developed a skin rash on the face that induced about 2 months later (fifth administration of P) the discontinuation of the biological drug (P). On June 2018, the patient developed panniculitis on the left forearm with oleocranic bursitis. Clinical evaluation revealed the absence of fever (36.5°C), while laboratory findings were in normal range (neutrophil 6,000 cell/mmc; normal range 2,500-7,700; PCT <0.5 ng/mL). Naranjo probability scale, [9] documented a possible association between Panitumumab and forearm disease (score 6), therefore an empirical antibiotic treatment with Ceftriaxone (1 gr bid) and ciprofloxacin (500 mg bid) plus a corticosteroid (methylprednisolone, 4 mg/day for 4 days) was started with a complete improvement of signs and symptoms in 2 weeks and without the development of adverse drug reactions or drug-drug interactions (Fig. **4**).

3. DISCUSSION

In this study, we reported the development of panniculitis in two women with metastatic colorectal cancer. Previously, several authors reported that many factors (*e.g.* drugs, allergy, bit of animals, parasites) are able to induce skin manifestations [10-14]. In our cases, clinical history suggested that probably Panitumumab could play a role in these skin manifestations.

Bergman *et al.* [15], in a retrospective study, documented that 32 of 34 patients treated with panitumumab developed a skin rash that required an antimicrobial treatment documenting an association between drug and adverse drug reaction.

Even if the specific mechanism of skin toxicity related to EGFR inhibitors has not been well demonstrated, some authors suggested that it could be related to the inhibition of EGFR in the basal lamina that induces a local inflammation,

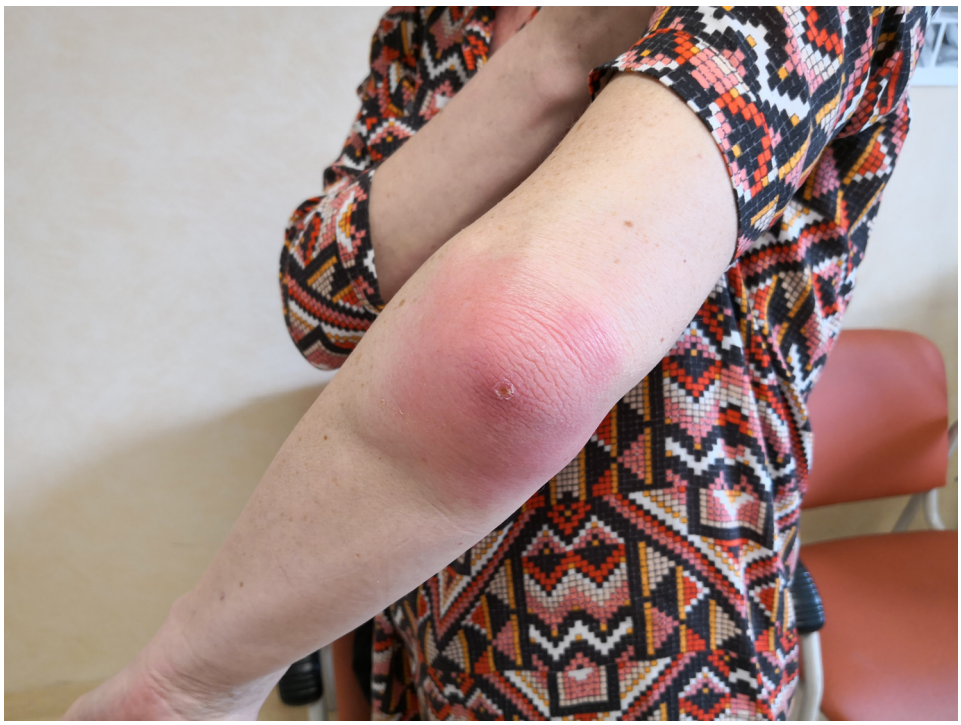

Fig. (4). Panniculitis in the second woman at the admission. It is possible to see the large area of erythema and olecranon bursitis at admission.

with the release of chemokines and leukocyte recruitment leading to keratinocyte apoptosis and skin damage [16, 17].

In an experimental study Liu *et al.* [18], documented that erlotinib hydrochloride induced skin toxicity proceeding from skin irritation to scleroderma and it was related to the inhibition of dermal EGFR with the development of skin inflammation and release of secondary inflammatory mediators (*e.g.* IL-10, IL-2, IL-6, TNF-α, and IL12A) prompting to skin toxicity.

In agreement with our previous studies [19-22], using the Naranjo probability scale, we documented a possible association between severe panniculitis and panitumumab in two women with mCRC (Naranjo score 6) that required a treatment with corticosteroids and empirical antimicrobial drugs.

Usually, the management of skin manifestations during EGFR inhibitors treatment is not fully standardized, however several recommendations based on small studies or case reports suggest a treatment with hydrocortisone 1% plus doxycycline (100 mg), twice a day, for the first 6 weeks (level II evidence) [23-25].

In contrast, in the present study considering the clinical characteristics of the patients (metastatic cancer and immune depression), we did not use tetracycline + topical corticosteroid but we preferred a more aggressive treatment with systemic corticosteroid + linezolid/ceftriaxone in a patient and systemic corticosteroid + ceftriaxone/ciprofloxacin in another patient with an improvement of symptoms.

This study has some limitations that are related to the type of the study (case report) and also the absence of skin biopsy.

However, it confirms that the development of skin toxicity represents a relevant problem during the treatment with EGFR inhibitors and that a treatment with corticosteroid and antimicrobials is able to improve clinical symptoms. In our institution, recently, we performed a study able to identify polymorphic variants associated with erlotinib-related skin toxicity that could be used to predict this severe adverse event in patients treated with anti-EGFR agents [26].

CONCLUSION

In conclusion, we reported for the first time the development of panniculitis during the treatment with Panitumumab and we documented that beta-lactams with fluoroquinolones or with oxazolidinone may be useful to improve symptoms in young patients with mCRC without the development of adverse drug reactions or drug interactions.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not Applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Written informed consent was obtained from both patients for this study.

STANDARD FOR REPORTING

The CARE guidelines and methodologies were followed in this study.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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All authors looked after the patient and wrote the report.

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