PAPULO-PUSTULAR FOLLICULAR ERUPTION DURING PANITUMUMAB TREATMENT OF COLON CANCER

VIRGIL PĂTRAȘCU*, LILIANA GABRIELA GEOLOAICA*

Summary

Introduction. *Epidermal growth factor receptor inhibitors (EGFR-I) are increasingly being used in the treatment of colorectal cancer, but not only. These drugs generally have good curative efficacy, but their skin-mucosal toxicity is recognized. We present cutaneous iatrogenic manifestations in a patient treated with Panitumumab (Vectibix) for stage IV colon cancer.*

Case report. *A 71-year-old patient attended the Dermatology Clinic of Craiova in august 2021 for a papulo-pustular rash, disseminated on the face and anterior thorax, the posterior cervical region and the scalp, where the existence of thick yellow-brown crusts is noticeable. The patient was diagnosed with splenic flexure colon cancer for which a segmental colectomy was performed (October 2020). Being in stage IV (cT4N2M1 with liver and lymph node metastases) palliative polychemotherapy (11 sequences) type CAPOX (capecitabine / oxaliplatin) was instituted for the period October 2020 – June 2021, then followed by palliative monochemotherapy with Capecitabine plus Panitumumab (6 mg / kg every two weeks). The papulopustular rash started 12 days after Panitumumab therapy.*

Discussions. *Due to the EGFR function on the skin, nails and hair, dermatological side effects are frequently seen after using EGFR-I (papulopustular rash, xerosis, pruritus, changes in nails, hair, mucous membranes).*

Conclusions. *The use of the new targeted therapy for oncological diseases is increasing. Papulo-pustular follicular eruptions are a complication of Panitumumab therapy, which often does not require discontinuation of treatment. Although the cutaneous side effects can be considered a biomarker for a favorable oncological result, they affect the quality of life of patients. It is important for dermatologists to recognize the symptoms and treat these manifestations to avoid discontinuation of treatment.*

Keywords: *colorectal cancer; EGFR-I; Panitumumab; papulo-pustular follicular eruption.*

Received: 03.12.2021 *Accepted: 06.01.2022*

Introduction

Colorectal cancer (CRC) is a major global health problem due to its high incidence, high treatment costs, and problems with reintegrating patients into society. About 11% of all cancers diagnosed in a year worldwide are located in the colon and rectum. The overall burden of CRC is expected to increase by 60% to over 2.2 million new cases and 1.1 million deaths annually by 2030. [1]

Epidermal growth factor receptor inhibitors (EGFR-I) are increasingly being for epithelial malignancies. These drugs have a good curative effect, but there is also therapeutic resistance to other cases. Although better tolerated than conventional therapy, this medication has unique side effect profiles that are related to their mechanism of action.

Due to the EGFR function on the skin, nails and hair, dermatological side effects are frequently observed after using EGFR-I (papulopustular rash, xerosis, pruritus, changes in nails, hair, mucous membranes). [2]

We present below the cutaneous iatrogenic manifestations found in a patient treated with Panitumumab (Vectibix) for stage IV colon cancer.

* Department of Dermatology, Emergency County Hospital, Craiova, University of Medicine and Pharmacy of Craiova, Romania.

Case report

A 71-year-old patient attended the Dermatology Clinic of Craiova in august 2021 for a papulo-pustular rash, disseminated on the face and anterior thorax, the posterior cervical region and the scalp, where the existence of thick yellow-brown crusts is noticeable. The patient was diagnosed with splenic flexure colon cancer for which a segmental colectomy was performed (October 2020). Being in stage IV (cT4N2M1 with liver and lymph node metastases) palliative polychemotherapy (11 sequences) type CAPOX (capecitabine/oxaliplatin) was instituted for the period October 2020 – June 2021, then followed by palliative monochemotherapy with Capecitabine plus Panitumumab (6 mg/kg every two weeks). The papulopustular rash started 12 days after Panitumumab therapy.

Past Medical History: Left colon neoplasm T4N2M1 (2020), grade I Hypertension, Chronic cholecystitis, Secondary anemia.

Living and working conditions: he worked as an electrician at the chemical plant.

Behaviors: Denies alcohol and smoking.

Medication: Indapamide 1.5 mg 1 cp/day, Tritace 5 mg 1 cp/day, Aspririne Cardio 75 mg 1 cp/day, Rosuvastatin 10 mg 1 cp/day, Silymarin 1 cp/day, Controloc 20 mg 1 cp/day, chemotherapy Panitumumab and Capecitabine (fluoropyridine).

Psysical examination: Phototype III, overweight (BMI 27.1), matte, friable nails, with onycholysis (Fig. 4).

Laboratory tests: elevated GOT 387 U/L, GPT 287 U / L, GGT 701 U/L, LDH 479 U/L (125-220), Hemoglobin 11.4 g/dl, erythrocytes 3.35 * 10^6/microl, platelets 146 * 10^3/microl, ESR 111 mm/h. The rest of the laboratory tests were within normal limits.

ALL-RAS-Genekor status: no mutations in NRAS or KRAS genes.

Genekor IHC: MLH1 and p53 were negative, MSH2, MSH6, PMS2 positive.

We performed a *mycological examination* (negative result) and a *bacteriological examination*, which was positive for Staphylococcus aureus in the impitiginized lesions of the scalp and negative for the rest.

We performed a *skin biopsy* comprising a group of pustules from the posterior cervical region, the histopathological examination showing infiltration of inflammatory cells in the dermis, especially in the upper part of the pillar follicle, with the appearance of neutrophil-suppurated folliculitis (Fig. 5).

Based on the anamnesis, the clinical examination, the laboratory analyzes and the criteria of imputability (chronological, semiological and notoriety) we specified the ***diagnosis*** of ***Iatrogenic papulo-pustular eruption induced by Panitumumab.***

General ***treatment*** was started with Sulcef (cefoperazone + sulbactam) 1 g every 12 hours, Diprogenta (betamethasone/gentamicin) cream on the scalp, Zineryt (erythromycin/zinc acetate) solution on the face, mixture with Erythromycin and Nystatin on the trunk . The evolution was favorable, the patient continuing the oncological treatment.

Discussions

CRC is more common among men than women and is 3-4 times more common in developed countries than in developing countries. The standardized incidence rate by age per 100,000 inhabitants is 19.7 for both sexes (23.6 for men and 16.3 for women). [1]

Developed countries have the highest risk of colon and rectal cancer. For colon cancer, Southern Europe, Australia/New Zealand and Northern Europe are the regions with the highest incidence. For rectal cancer, these regions are Eastern Europe, Australia/New Zealand and East Asia. North America is also among the countries with the highest incidence rates for both cancers. CRC is the third leading cause of cancer death in the world, and its incidence is steadily rising in developing countries that adopt a „Western" way of life. [1]

Romania, according to GLOBOCAN, in 2020, the number of diagnosed cancers, regardless of location, was 98886, of which 12938 (13.1%) were located in the colon and rectum, occupying the first place, thus surpassing lung cancer (12.3%) and breast cancer (12.2%). In the same year, 6767 patients with CRC died, ranking second after deaths caused by lung cancer.

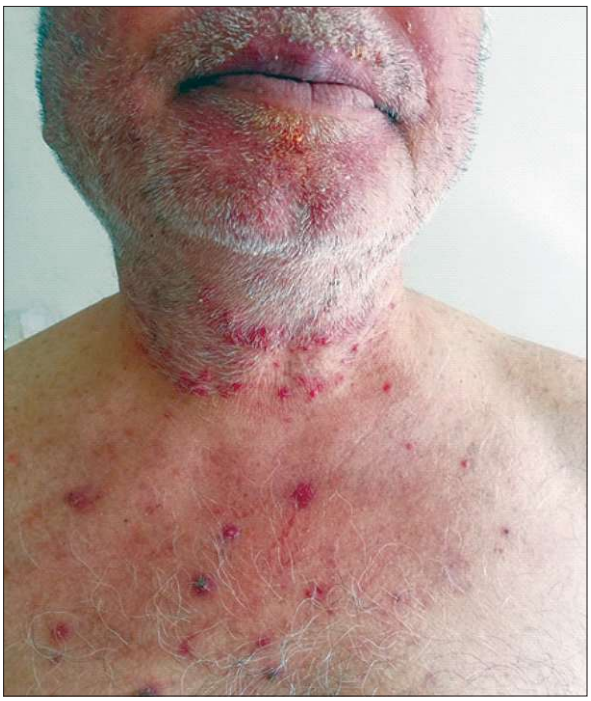

Figure 1 – Papulo-pustular eruption induced by Panitumumab.

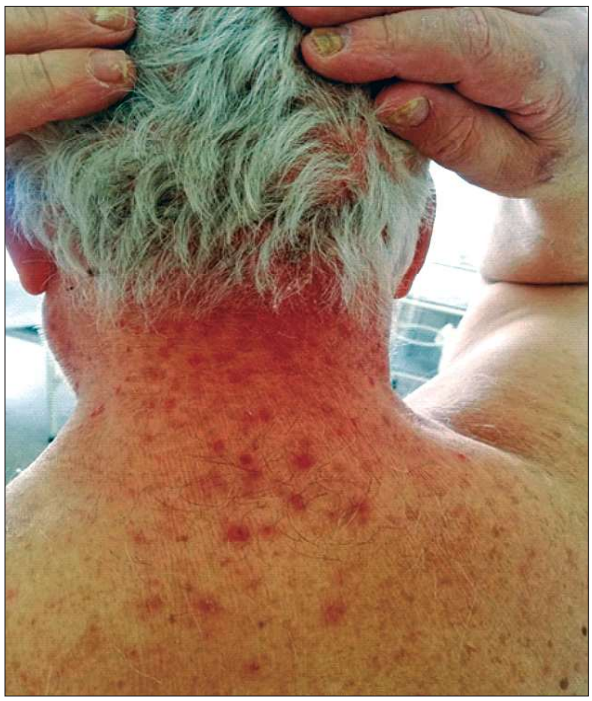

Figure 2 – Papulo-pustular eruption induced by Panitumumab.

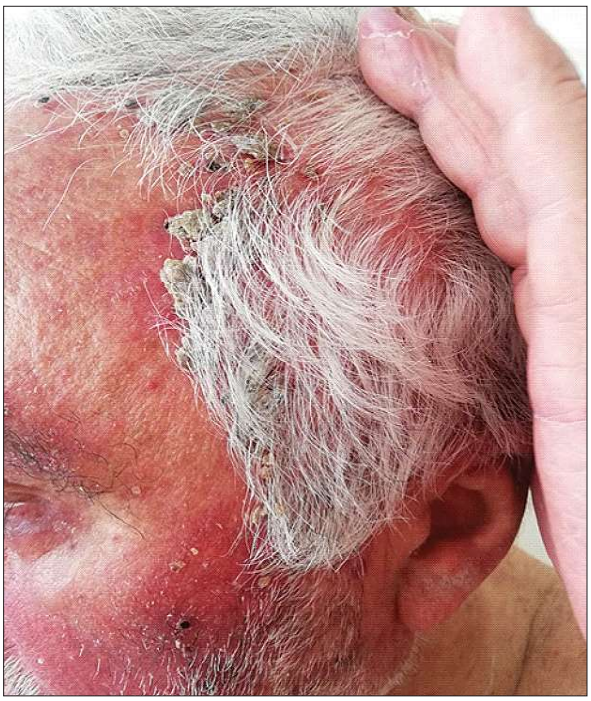

Figure 3 – Papulo-pustular eruption (impetiginized) induced by Panitumumab.

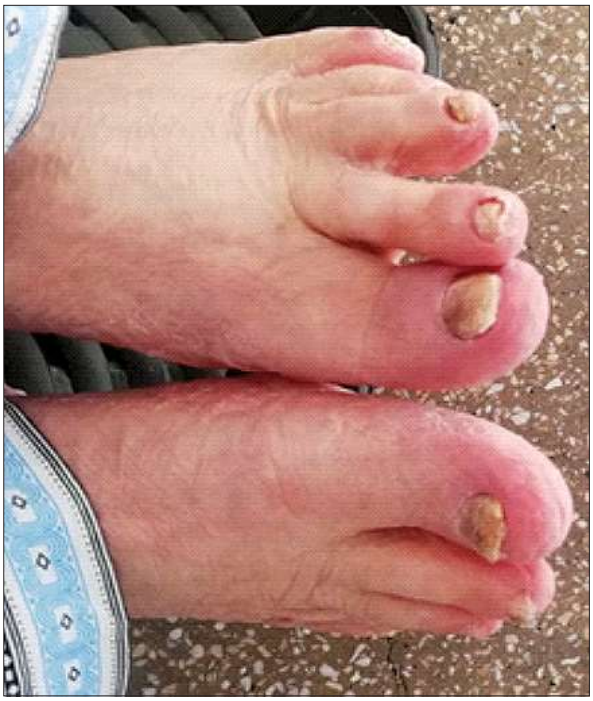

Figure 4 – Iatrogenic onychodystrophy in a patient with colon cancer (stage IV).

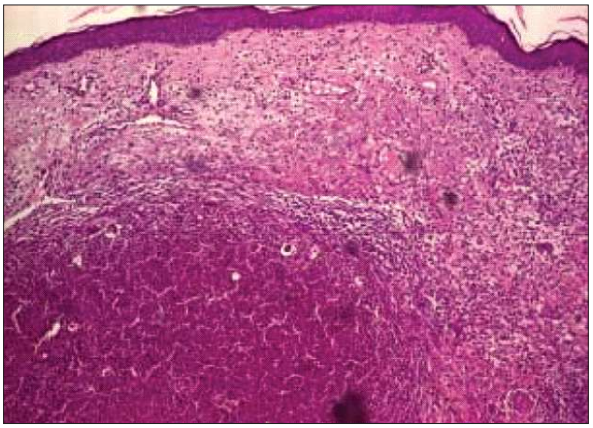

Figure 5 – Inflammatory cell infiltrate in the dermis, especially in the upper part of the hair follicle (appearance of suppurative folliculitis with neutrophils) (H&E M 40).

Globally, CRC is the third most commonly diagnosed cancer in men and the second most common in women, according to the World Health Organization's GLOBOCAN database. Both incidence and mortality rates are substantially higher in men than in women. [3] Obesity, sedentary lifestyle, consumption of red meat, alcohol and tobacco are considered, along with genetic predisposition, the main factors underlying the increase in the incidence of CRC.

Advances in understanding the pathophysiology of this cancer have led to increased treatment options, including endoscopic and surgical excision, radiation therapy, immunotherapy (Pembrolizumab, Nivolumab, Ipilimumab, etc.), palliative chemotherapy, targeted therapy, and for metastases extensive surgery and local ablative therapies. Unfortunately, approximately 20% of new cases are diagnosed with metastatic colorectal cancer (mCRC) at the time of the initial visit, negatively affecting the prognosis.[4] Subsequently, 40-50% of people with early-stage disease develop metastases, which contribute to the increased mortality rate associated with CRC.

The prognosis depends on the stages of the disease. A French study reported a 5-year survival rate of 82% for patients in stage I-II, compared with only 7.6-9.6% for stage IV disease.

Also known as colorectal adenocarcinoma, this cancer usually develops in the glandular epithelial cells of the large intestine.[5] Other uncommon cancers of the colon are carcinoid tumors, gastrointestinal stromal tumors, lymphomas, and sarcomas. [4] Epithelial cancers are characterized by mutations in growth factor and growth factor receptor, giving them the potential for uninhibited cell proliferation, migration, and promoting angiogenesis. [2]

EGFR-I are able to inhibit this signaling. Panitumumab and Cetuximab are monoclonal antibodies that target this receptor and have clinical activity in patients with mCRC,[6, 7]

There are two general classes of EGFR-I:

- ✓ anti-EGFR monoclonal antibodies: panitumumab, cetuximab and necitumumab;
- ✓ EGFR small molecule tyrosine kinase inhibitors (Tki): Tki (gefitinib and erlotinib) and additional Tki (lapatinib, afatinib, neratinib, vandetanib), which inhibit multiple receptors. [2, 8]

EGFR-I are currently approved to treat colorectal cancer, but can also treat small cell lung cancer, squamous cell carcinoma of the head and neck, pancreatic cancer, and breast cancer. [2, 9]

Due to the presence of EGFR in the basal cells of the epidermis, hair, sebaceous glands, side effects are common. [10, 11] These skin toxicities may reduce or discontinue therapy, in addition to affecting quality of life. It is therefore important to recognize and effectively manage these side effects. [12, 13]

An EGFR-I-induced rash correlates with better overall survival without cancer progression. Therefore, ideally, treatment with EGFR-I is continued even in the presence of certain skin toxicities, as skin side effects are an indication of an effective response. [14, 15]

Panitumumab is a fully human monoclonal antibody indicated for the treatment of metastatic colorectal cancer that has a wild-type (non-mutant) RAS gene:

- ✓ as first-line treatment, in combination with FOLFOX (folinic acid/5-fluorouracil/oxaliplatin) or FOLFIRI (folinic acid/5-fluorouracil/irinotecan);
- ✓ as second-line treatment, in combination with FOLFIRI, in patients receiving first-line fluoropyrimidine chemotherapy (excluding irinotecan);
- ✓ as monotherapy, after failure of fluoropyrimidine, oxaliplatin, irinotecan regimens. [16]

Dermatological side effects are commonly seen after using EGFR-I and include:

➢ **papulo-pustular rashes**

Also called acneiform or acneiform-like rashes, they are the earliest and most common side effects and affect 20-80% of patients treated with EGFR-I. The rash may appear between 2 days and 6 weeks after the first administration of the drug, but it usually develops in the first 2 weeks, a situation that is also present in our case. [17, 18, 19]

Clinically, they are characterized by sensitive erythematous papules, which turn into pustules and then crusts. Affects areas of the skin with a high frequency of sebaceous glands (scalp, face, upper torso), less often may involve the extremities, lower back, abdomen. The lesions may be painful or itchy. [20]

Histologically, 2 major reaction patterns have been described:

- hyperkeratosis or ectatic follicular infundibulum surrounded by an infiltrate with superficial dermal inflammatory cells, especially in the upper part of the hair follicle;
- neutrophil suppurative folliculitis and rupture of the epidermal lining.

No changes in dermal capillaries, eccrine or sebaceous glands have been described. Microbiological cultures have shown no infection, confirming that this is a sterile process. [21]

Unlike acne vulgaris, there is no hypertrophy of the sebaceous glands, comedones, or inflammatory infiltrate associated with Propionbacterium acnes colonization. [22]

The lesions can be complicated by impetigo, present in the scalp in our case, which must be suspected when a sudden aggravation of the rash occurs. [20]

The table 1 the severity of papulopustular eruptions, our patient having grade I, according to this classification. [23]

➢ **nail changes**

They are commonly seen as side effects of EGFR-I, with a described incidence of 17.2% in one study. [24]

These changes include paronychia and lesions similar to pyogenic granuloma, with erythema and tenderness of the skin adjacent to the nail.

Other changes include thin, easily broken nails, as well as onycholysis, with nail detachment from the nail bed and nail discoloration due to the involvement of the nail matrix. [25]

➢ **xerosis and pruritus**

It often resembles atopic dermatitis or may look like Craquelé eczema. It can lead to fissures. In a study that evaluated the impact of

Table 1. *National Cancer Institute Common Terminology Criteria for Adverse Events*

Classification	Characteristics
Grade I	- papules and / or pustules covering <10% of body surface area with or without symptoms of pruritus or tenderness
Grade II	- papules and / or pustules covering 10-30% of the body surface, whether or not associated with symptoms of pruritus or tenderness; psychosocial impact; limiting daily instrumental activity
Grade III	- papules and / or pustules covering> 30% of the body surface, whether or not associated with pruritus or tenderness; limitation of daily self-care activity associated with local superinfection (oral antibiotics indicated)
Grade IV	- covering any percentage of the body surface, whether or not associated with pruritus or tenderness; associated with severe superinfection (intravenous antibiotics indicated); life-threatening consequences
Grade V	- death.

dermatological events on quality of life, it was found that xerosis and pruritus are the most significant adverse events described. [26] Pruritus occurred in 17-58% of patients treated with EGFR-I, the highest frequency being in those treated with panitumumab. [27]

- **hair changes**

They are commonly seen with prolonged EGFR-I therapy. Patients may experience mild hair loss and changes in hair texture, as well as circumscribed scarring / non-scarring alopecia. Eyelashes can suffer from a process of trichomegaly that can cause blepharitis. Eyebrow poliosis, with loss of pigment and subsequent bleaching of the hair, has also been described. Hirsutism was sometimes observed on the face. [28, 29]

- **changes in the oral, ocular and genital mucous membranes**

Patients may have multiple ulcers or oral aphthae. A viral infectious etiology (Varicella Zoster Virus, Herpes Simplex Virus) should be ruled out. Xerosis and geographic language may occur.

Ocular manifestations include keratitis, conjunctivitis, and vulvovaginitis or balanitis may occur in the genitals. [30]

- **photosensitive eruptions** have been described as a side effect of EGFR-I therapy.

Interestingly, the typical papulopustular eruption tends to favor areas exposed to the sun, such as the face and V-neck. In addition, radiodermatitis can be exacerbated by concomitant EGFR-I therapy and radiation therapy. [31]

- **severe eruptions, Stevens-Johnson syndrome and Toxic epidermal necrolysis** are rare.

In a study of 8,998 patients treated with EGFR-I, there were no deaths due to cutaneous eruptions. [32, 33]

Treatment

Treatment is conceived to prevent dose reduction or stopping anticancer therapy. However, for life-threatening or serious side effects, dose reduction or treatment discontinuation is required.

Preventive measures: moisturizing xerotic skin 2 times/day with emollients, non-alcoholic urea creams, sunscreen, avoiding hot showers, frequent hand washing, avoiding contact with irritants (solvents, disinfectants, varnishes).

Prophylaxis with tetracycline, minocycline or doxycycline resulted in decreased frequency and severity of skin adverse reactions. [34]

Tromkova et al. evaluated the possible effect of local pre-treatment with phytomenadione (vitamin K1) on decreasing the extention and severity of follicular rash (menadione stabilizes EGFR phosphorylation). [35]

Mild toxicity: local steroid (hydrocortisone 1-2.5% cream) or clindamycin gel 1%. Alternatives: erythromycin 3% gel/cream, metronidazole 0.75-1% cream/gel.

Moderate toxicity: local steroid, clindamycin (1% gel), pimecrolimus (1% cream) plus doxycycline (100 mg * 2/day), minocycline (100 mg * 2/day).

Severe toxicity: treatment of moderate toxicity plus metiprednisolone and treatment of superinfections (antibiogram required). [36] Alternatives: isotretinoin 0.3-0.5 mg/kg/day. [37]

If the cutaneous eruption is not reduced after 2-4 weeks of treatment, discontinuation/ reduction of therapy is recommended.

In a study (Gabriella Fabbrocini et al., Italy) from October 2010-July 2014 on 80 patients treated with EGFR-I (cetuximab, erlotinib, lapatinib, gefitinib, panitumumab), 80% had a papulopustular rash, 20 % nail changes, 45% alopecia, 1% trichomegaly, 30% paronychia. The papulo-pustular rash was located on the face, neck, back of the ear, scalp, upper torso, but also involved the abdomen, arms, legs. Most patients had a mild to moderate rash (grade I, II) but 4 patients developed a grade III rash. The treatment included a mixture of Clindamycin gel 1% and gentamicin 0.1% ointment one or two applications / day. The lesions healed completely in 2 weeks for a mild, moderate rash. In more severe eruptions, prednisone was administered 12.5-25 mg / day for one week, with a gradual decrease in dose. [38]

Conclusions

The use of the new targeted therapy for oncological diseases is increasing. Follicular papulo-pustular eruptions are a complication of Panitumumab therapy, which often does not require discontinuation of this treatment.

Although skin side effects can be considered a biomarker for a favorable oncological result, they affect the quality of life of patients.

It is important for this reason that dermatologists recognize the symptoms and treat these manifestations to avoid discontinuation of treatment.

Bibliography

1. Prashanth Rawla, Tagore Sunkara, Adam Barsouk. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. *Prz Gastroenterol.* 2019; 14(2): 89–103.
2. Ciardiello F, Tortora G. EGFR antagonists in cancer treatment. *N Engl J Med.* 2008;358(11):1160–1174.
3. Finlay A Macrae. Colorectal cancer: Epidemiology, risk factors, and protective factors. Literature review current through: Nov 2021.
4. Yue Xi, Pengfei Xu. Global colorectal cancer burden in 2020 and projections to 2040. *Transl Oncol* 2021 Oct;14(10):101174
5. Alexandros A Tzovaras , Athanassios Karagiannis, Charalambia Margari, Georgi Barla, Alexandros Ardavanis. Effective panitumumab treatment in patients with heavily pre-treated metastatic colorectal cancer: a case series. *Anticancer Res.* 2011 Mar;31(3):1033-7.
6. Qing-Hai Li, Ying-Zhao Wang, Jian Tu, Chu-Wei Liu, Yu-Jie Yuan, Run Lin, Wei-Ling He, Shi-Rong Cai, Yu-Long He, Jin-Ning Ye. Anti-EGFR therapy in metastatic colorectal cancer: mechanisms and potential regimens of drug resistance. Gastroenterology Report, Volume 8, Issue 3, June 2020, Pages 179–191 .
7. Francesca Battaglin, Alberto Puccini, Selma Ahcene Djaballah, Heinz-Josef Lenz. The impact of panitumumab treatment on survival and quality of life in patients with RAS wild-type metastatic colorectal cancer. *Cancer Manag Res.* 2019; 11: 5911–5924.
8. Harari PM, Allen GW, Bonner JA. Biology of interactions: antiepidermal growth factor receptor agents. *J Clin Oncol.* 2007;25(26):4057–4065.
9. Nolting M, Schneider-Merck T, Trepel M. Lapatinib. *Recent Results Cancer Res.* 2014;201:125–143.
10. Green MR, Couchman JR. Differences in human skin between the epidermal growth factor receptor distribution detected by EGF binding and monoclonal antibody recognition. *J Invest Dermatol.* 1985;85(3):239–245.
11. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. *Nat Rev Cancer.* 2006;6(10):803–812.
12. Rosen AC, et al. Impact of dermatologic adverse events on quality of life in 283 cancer patients: a questionnaire study in a dermatology referral clinic. *Am J Clin Dermatol.* 2013;14(4):327–333.
13. Osio A, et al. Cutaneous side-effects in patients on long-term treatment with epidermal growth factor receptor inhibitors. *Br J Dermatol.* 2009;161(3):515–521.
14. Abdel-Rahman O, Fouad M. Correlation of cetuximab-induced skin rash and outcomes of solid tumor patients treated with cetuximab: a systematic review and meta-analysis. *Crit Rev Oncol Hematol.* 2015;93(2):127–135.
15. Liu HB, et al. Skin rash could predict the response to EGFR tyrosine kinase inhibitor and the prognosis for patients with non-small cell lung cancer: a systematic review and meta-analysis. PLoS One. 2013;8(1):e55128.
16. Keating GM. Panitumumab: a review of its use in metastatic colorectal cancer. *Drugs* 2010;70:1059–1078.
17. Mittmann N, Seung SJ. Rash rates with EGFR inhibitors: meta-analysis. *Curr Oncol.* 2011;18(2):e54–63.
18. Lacouture ME, et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Support Care Cancer.* 2011;19(8):1079–1095.
19. Virgil Pătraşcu, Florentina Delcea, Raluca Niculina Ciurea, Corneliu Cristian Georgescu, Andreea Oana Enache. Papulopustular follicular eruption caused by cetuximab-two clinical cases. *Romanian Journal of Clinical and Experimental Dermatology* 3-4/2016: 158-162.
20. Peuvrel L, Bachmeyer C, Reguiai Z, Bachet JB, André T, Bensadoun RJ, Bouché O, Ychou M, Dréno B. Semiology of skin toxicity associated with epidermal growth factor receptor (EGFR) inhibitors. *Support Care Cancer.* 2012;20:909–921.
21. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. *Nat Rev Cancer.* 2006;6:803–812.
22. Gridelli C, Maione P, Amoroso D, Baldari M, Bearz A, Bettoli V, Cammilluzzi E, Crinò L, De Marinis F, Di Pietro FA, Grossi F, Innocenzi D, Micali G, Piantedosi FV, Scartozzi M. Clinical significance and treatment of skin rash

from erlotinib in non-small cell lung cancer patients: results of an Experts Panel Meeting. *Crit Rev Oncol Hematol.* 2008;66:155–162.
23. Chanprapaph K, Vachiramon V, Rattanakaemakorn P. Epidermal growth factor receptor inhibitors: a review of cutaneous adverse events and management. *Dermatol Res Pract.* 2014;2014:734249.
24. Garden BC, Wu S, Lacouture ME. The risk of nail changes with epidermal growth factor receptor inhibitors: a systematic review of the literature and meta-analysis. *J Am Acad Dermatol.* 2012;67(3):400–408.
25. Robert C, et al. Nail toxicities induced by systemic anticancer treatments. *Lancet Oncol.* 2015;16(4):e181–189.
26. Clabbers JM, et al. Xerosis and pruritus as major EGFRI-associated adverse events. *Support Care Cancer.* 2016;24(2):513–521.
27. Ensslin CJ, et al. Pruritus in patients treated with targeted cancer therapies: systematic review and meta-analysis. *J Am Acad Dermatol.* 2013;69(5):708–720.
28. Fabbrocini G, et al. Trichomegaly of the eyelashes during therapy with epidermal growth factor receptor inhibitors: report of 3 cases. *Dermatitis.* 2012;23(5):237–238.
29. Rodriguez NA, Ascaso FJ. Trichomegaly and poliosis of the eyelashes during cetuximab treatment of metastatic colorectal cancer. *J Clin Oncol.* 2011;29(18):e532–3.
30. Busam KJ, et al. Cutaneous side-effects in cancer patients treated with the antiepidermal growth factor receptor antibody C225. *Br J Dermatol.* 2001;144(6):1169–1176.
31. Luu M, et al. Photosensitive rash due to the epidermal growth factor receptor inhibitor erlotinib. *Photodermatol Photoimmunol Photomed.* 2007;23(1):42–45.
32. Doesch J, et al. Afatinib-associated Stevens–Johnson syndrome in an EGFR-mutated lung cancer patient. *Lung Cancer.* 2016;95:35–38.
33. Huang JJ, et al. Toxic epidermal necrolysis related to AP (pemetrexed plus cisplatin) and gefitinib combination therapy in a patient with metastatic non-small cell lung cancer. *Chin J Cancer.* 2015;34(2):94–98.
34. Hofheinz RD, et al. Recommendations for the prophylactic management of skin reactions induced by epidermal growth factor receptor inhibitors in patients with solid tumors. *Oncologist.* 2016;21(12):1483–1491.
35. Tomková H, Pospíōková M, Zábojníková M, Kohoutek M, Serclová M, Gharibyar M, Sternberský J. Phytomenadione pre-treatment in EGFR inhibitor-induced folliculitis. *J Eur Acad Dermatol Venereol.* 2013;27:514–519.
36. Micantonio T, Fargnoli MC, Ricevuto E, et al. Efficacy of treatment with tetracyclines to prevent acneiform eruption secondary to cetuximab therapy. *Arch Dermatol.* 2005; 141: 1173–1174.
37. Gutzmer R, et al. Successful treatment with oral isotretinoin of acneiform skin lesions associated with cetuximab therapy. *Br J Dermatol.* 2005; 153(4): 849–851.
38. Gabriella Fabbrocini, Luigia Panariello, Gemma Caro, and Sara Cacciapuoti. Acneiform Rash Induced by EGFR Inhibitors: Review of the Literature and New Insights. *Skin Appendage Disord.* 2015 Mar; 1(1): 31–37.

Conflict of interest

NONE DECLARED

Correspondance addresses: Professor, MD, PhD Virgil Pătrașcu
Department of Dermatology, University of Medicine and Pharmacy of Craiova
Petru Rareș Street, No 2-4, 200345, Craiova, Romania,
E-mail: vm.patrascu@gmail.com