Cutaneous manifestations of new oncologic drugs: epidermal growth factor receptor inhibitors and 5-fluorouracil prodrugs

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Abstract

In recent years, novel drugs have been incorporated into cancer therapy. They include capecitabine, an oral 5-fluorouracil prodrug (used in metastatic colorectal and breast carcinoma), and epidermal growth factor receptor inhibitors such as cetuximab and lapatinib. These drugs have a high incidence of cutaneous side effects. Capecitabine produces a reaction in palms and soles known as hand-foot syndrome or erythrodysesthesia, and skin pigmentation. Cetuximab effects include an acneiform eruption (marker of therapeutic efficacy), and nail and hair abnormalities. We present six patients treated with these drugs are presented. Four of them received capecitabine and showed different stages of hand-foot syndrome, nail dystrophy, and eruptive appearance of lentiginous lesions, mainly on in palms and soles. The histopathology of these pigmentary lesions showed basal hyperpigmentation with lentiginous pattern. The other two patients received cetuximab for colorectal adenocarcinoma and showed an early follicular papulo-pustulous eruption dominant on trunk and head, typical of EGFR inhibitors, and later, various levels of nail dystrophy and hair abnormalities. Treatment of side effects of these cytostatic drugs is currently not standardized, and in some cases requires dose reduction, or drug discontinuation. We wish to stress how important it is for the dermatologist to know the cutaneous effects of these, drugs for its adequate diagnosis and treatment, thus avoiding unnecessary discontinuation, and improving the patient's quality of life. Likewise, we point out that eruptive lentiginosis, and hair curling are rarely mentioned in the literature (Dermatol Argent 2008;14(4):281-287).

Key words: *cetuximab, capecitabine, epidermal growth factor, eruptive nevi, acneiform eruption.*

Introduction

In recent years, novel drugs have been incorporated into various types of cancer therapy, with specific cutaneous side effects. This new arsenal includes target therapies with epidermal growth factor receptor inhibitors (IEGFR), whose main cutaneous side effect is an acneiform reaction of different severity (**Table 1**). Other recently incorporated drugs are 5-fluorouracil prodrugs, whose limiting cutaneous toxicity is the hand-foot syndrome or erythrodysesthesia (**Table 2**). Six patients treated with these drugs are presented; they have been seen at the Dermatology Department of Hospital Alemán for the last five months, and have shown the described dermatologic effects of these drugs, some rarely reported in the literature.

Clinical cases

Case 1

A 59-year-old male with metastatic colorectal adenocarcinoma treated with cetuximab and capecitabine. Ten days after starting chemotherapy, an erythematous, papulo-pustulous eruption appeared in seborrheic areas, associated with burning and itching. Biopsy of one of the pustules shows dense neutrophilic inflammatory infiltrate in intermediate and deep dermis, with perifollicular dominance and destruction of the pilosebaceous

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follicle. After 40 days, erythema, xerosis, and shedding of the plate also occured, with appearance of pyogenic granuloma on several fingers (**Figure 1**), eyebrow and eyelash trichomegaly, and curling of the hair. Progressive occurrence of 2 to 3 mm diameter nevi was observed on palms and soles.
He was treated with minocycline 100 mg/day, humectation, and photo-protection, with remarkable improvement of the acneiform reaction and of nail involvement.

Case 2

A 76-year-old male with metastatic colorectal adenocarcinoma treated with irinotecan and cetuximab. After the first cycle he showed the same follicular eruption (**Figure 2**), nail xerosis, nail striations and curling of the scalp hair. The histopathological, exam of a papulo-pustulous lesion showed an epidermal pustule comprising polymorphonuclear cells. In another sector of the sample, an intra-follicular abscess with destruction of the pilosebaceous unit was seen (**Figure 3**). Topic treatment with corticosteroids and fusidic acid, systemic antihistamines, humectation, and photo-protection was started, with improvement of the lesions.

Case 3

A 47-year-old female treated with capecitabine and docetaxel for metastatic breast carcinoma. Two months after initiating therapy, mucositis and erythema, burning pain, paresthesia and xerosis appeared on palms and soles, compatible with grade 2 hand-foot syndrome. Six months later, she developed hand and foot nail onycholysis and two shades of brown macules of 3 to 9 mm on palms and soles of sudden appearance (**Figure 3**). The histopathological test of a pigmented palm lesion reported epidermis with moderate inter-papilar crest acanthosis and increased amount of mature pigmented melanocytes, compatible with simplex lentigo.

Case 4

A 55-year-old female patient with metastatic breast carcinoma treated with capecitabine and lapatinib. One month later, a Grade 2 hand-foot syndrome occurred, that improved with humectation and appropriate shoes. Likewise, 2 to 3 mm diameter lentigines appeared suddenly on trunk and limbs (**Figure 5**). Some lesions were found on palatine mucosa. The histopathological exam of a palm lesion was similar to case 3 (**Figure 6**).

Case 5

A 83–year-old male patient, treated with capecitabine for a colon adenocarcinoma, presented with hyperpigmentation and fissured keratoderma. Appearance of 2 to 10 mm diameter brown macules on palms and soles in the last two months was ascertained. The histopathological study was similar to those of the preceding cases.

Case 6

A 34-year-old female with liver metastasis of colon carcinoma treated with capecitabine and bevacizumab. Presented with grade 2-3 hand-foot syndrome, which improved with humectation and general care measures. In the last month, she developed eruptive lentigos on palms and soles. No skin biopsy was performed due to patient refusal.

TABLE 1. SEVERITY CLASSIFICATION OF ACNEIFORM REACTION.

	Version 2	Version 3
Grade 1	Asymptomatic eruption	No treatment needed
Grade 2	Symptomatic lesions affecting less than 50 percent of body surface	Requires treatment
Grade 3	More than 50 percent of body surface affected	Presence of pain, defiguration, ulceration, or shedding
Grade 4	Exfoliating erythroderma	

TABLE 2. SEVERITY CLASSIFICATION OF HAND-FOOT SYNDROME

	NCI classification	WHO classification
Grade 1	Erythema, edema, shedding, and dysesthesias	Dysesthesias and erythema
Grade 2	Additional pain and slight interference with daily activities	Erythema and edema, pain when grasping objects or in walking
Grade 3	Presence of ulcers, blisters, bleeding	Additional periungual compromise and fissures
Grade 4	Severe shedding or pain with important interference with activities	Additional blisters, ulcers and severe pain, making walking or use of hands difficult

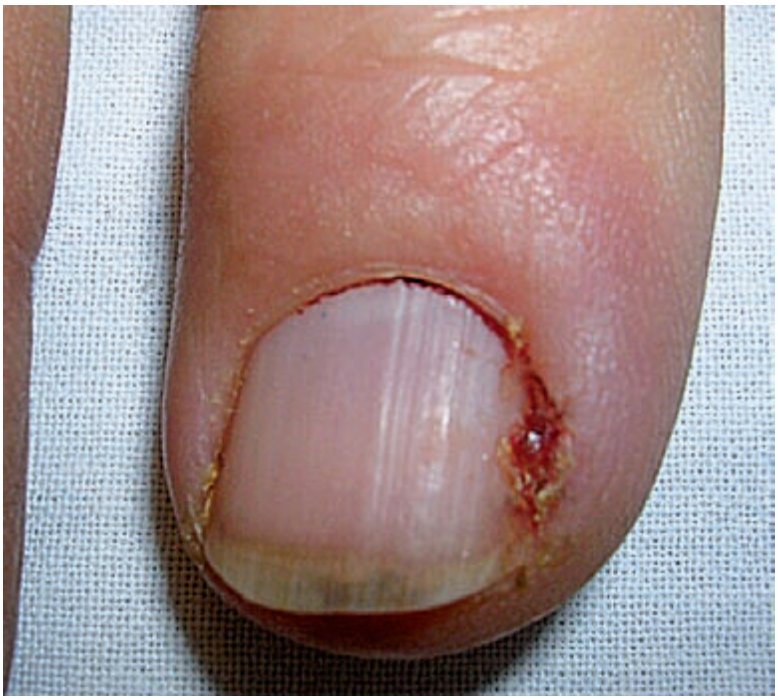

Figure 1. *Perionyxis with pyogenic granuloma on index finger.*

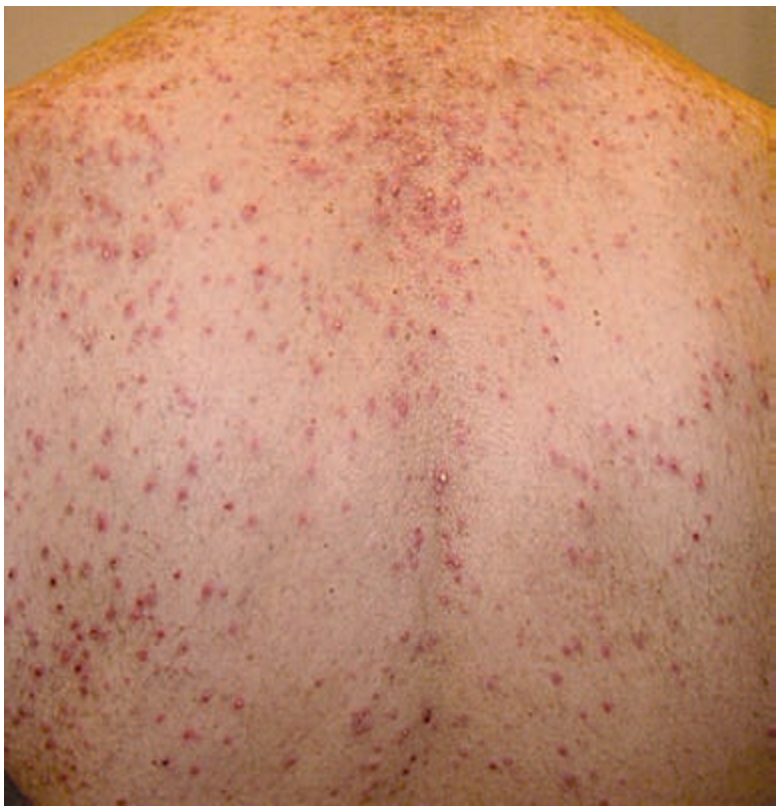

Figure 2. *Acneiform reaction on the back.*

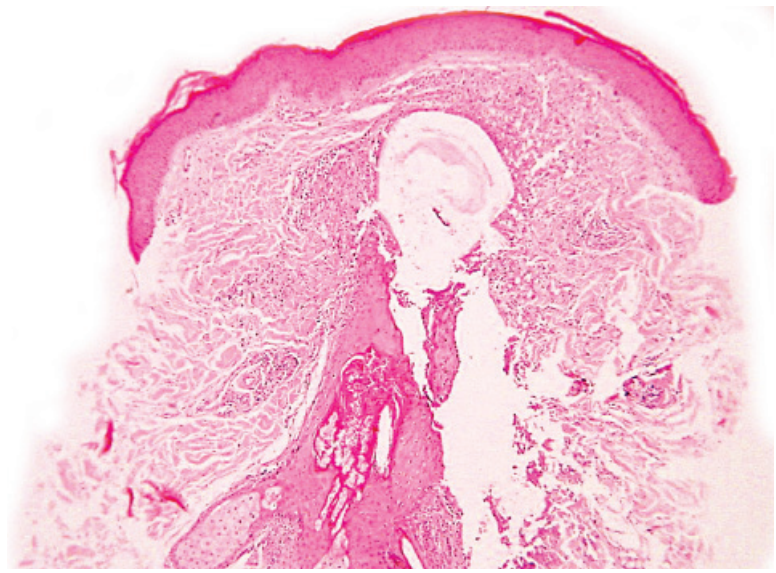

Figure 3. *Pustule with destruction of pilosebaceous unit is identified with low magnification (10x).*

Discussion

Epidermal growth factor receptor inhibitors

Epidermal growth factor receptor (EGFR or ErbB-1/HER1) is a 170 kDa transmembrane protein with an extracellular domain, a transmembrane domain, and an intracellular tyrosine kinase (TK) domain. After binding to its ligand, activation of a transduction signal cascade regulating proliferation, maturity, migration, survival, cell apoptosis and angiogenesis occurs.[1-3] This receptor is expressed in normal cells of several organs, including skin, and is responsible for maturity, differentiation, and survival of keratinocytes.[1,4,5] Usually it is expressed in up to 90 percent[6] of diverse solid tumor cell lines.

Inhibitors of epidermal growth factor receptor (IEGFR) are separated into two groups:

- **Monoclonal antibodies**. Cetuximab (Erbitux®) is a human-murine chimeric antibody approved by FDA in 2004 for metastatic colorectal carcinoma (CRC) refractory or intolerant to other chemotherapies, and for advanced or metastatic squamous carcinoma of head and neck non-responding to cisplatino.[1,7]
- **TK inhibitors**. Low molecular weight compounds which inhibit this part of the receptor, preventing phosphorilation.[2] They include gefitinib (Iressa®), erlotinib (Tarceva®), lapatinib (Tykerb®), and canertinib.

Adverse effects

Adverse effects of IEGFRs are similar for both groups. There is increasing evidence in favor of them being dose-dependant and that their presence and severity correlates with a better anti-tumor response, and a greater survival.[8] Cutaneous reactions are found in sites of high EGFR expression, and include papulo-pustulous eruptions, paronychia, hair growth abnormalities, itching, and xerosis, under the acronym PRIDE (*papulo-pustules and/or paronychia, regulatory abnormalities of hair growth, itching and dryness*).[9]

Acneiform or papulo-pustulous **eruption**: constitutes the most frequent side effect of these drugs. It is dose-dependant. It appears with cetuximab in 85 percent, with erlotinib in 75 percent, and with gefitinib in 55 percent.[3,5,8] It affects seborrheic areas: face, shoulders, upper trunk area, and scalp, but occasionally spreadind to other areas.[10,8] More frequent, precocious, and disseminated with cetuximab.

Lesions consist of follicular and inter-follicular papules and pustules,[4] isolated or aggregated, on an erythematous base, together with itching and formation of yellowish squamous crusts, that occasionally gives them a seborrheic dermatitis-like appearance.[11] A very intense erythema mimicking erysipelas rarely occurs, or inflammation can be so severe that it may cause necrosis and tissue ulceration.[8] Hemorrhagic lesions have been reported.[12]

Typically, it is seen within the first 14 days of starting drug administration; it can also get worse after

each infusion and disappear weeks after treatment is stopped. In many cases, gradual improvement occurs spontaneously, even if the treatment ins`t stopped. It may be triggered by sun exposure.[6] Pustules are sterile and only seldom *Staphylococcus aureus* was isolated, considering it a superinfection.

National Cancer Institute (NCI) criteria are used to classify its severity (NCI);[8] two current criteria version exist, known as version 2 and version 3 (version 1 is no longer used). Version 2 takes the clinical aspects into account, and version 3, therapeutics (**Table 1**). These classifications are partial and scarcely precise, and new severity scales are in proecess.[6]

Histopathology. Suppurative neutrophilic inflammatory infiltrate is observed, affecting the pilosebaceous follicle with obstruction, dilation and follicular destruction. There is epidermal hyperkeratosis with loss of the normal basket pattern and occasional intra-epidermal or eccrine duct acantholysis,[8] apoptotic keratinocytes, basal vacuolar degeneration, and lichenoid reaction.[1] There are some descriptions of the presence of multinucleated giant cells in the infiltrate.[13]

The effects of IEGFR on cell maturity and growth (demonstrated increase of p27 increase and reduction of Ki67 levels)[1,8] would be responsible for this eruption, causing pilosebaceous unit disorganization with hyperkeratosis, follicle obstruction and degeneration, pro-inflammatory cytokine release, infundibular microflora alteration, and sebaceous material diffusion to dermis.[8]

Nail apparatus alterations. They are the second most frequent cutaneous side effect (6 to 50 percent) and constitute a late event brginning one to six months after treatment onset. Perionyxis with erythema, edema, and painare the most frecuent alterations.[14] They may be very severe and produce onychocryptosis-like appearance, and pyogenic granuloma or abscess formation. *S. aureus* or other microorganisms superinfection is common. The nail plate is more fragile, glossy, and slow-growing. It is associated with xerosis, shedding and periungual fissures, cuticle and plate rupture, and partial onycolysis.[15-17]

Hair growth abnormalities[2,3,16,18] (18 percent). They appear later, from 2 to 6 months after treatment onset and usually disappear a month after treatment has been completed. They consist of the lengthening (trichomegaly), thickening, and curving of eyelashes and eyebrows.[19] Beard grows more slowly and moderate scalp alopecia may be seen. With time, facial[8] or generalized hypertrichosis usually occur. Scalp hair tends to curl or become straighter.

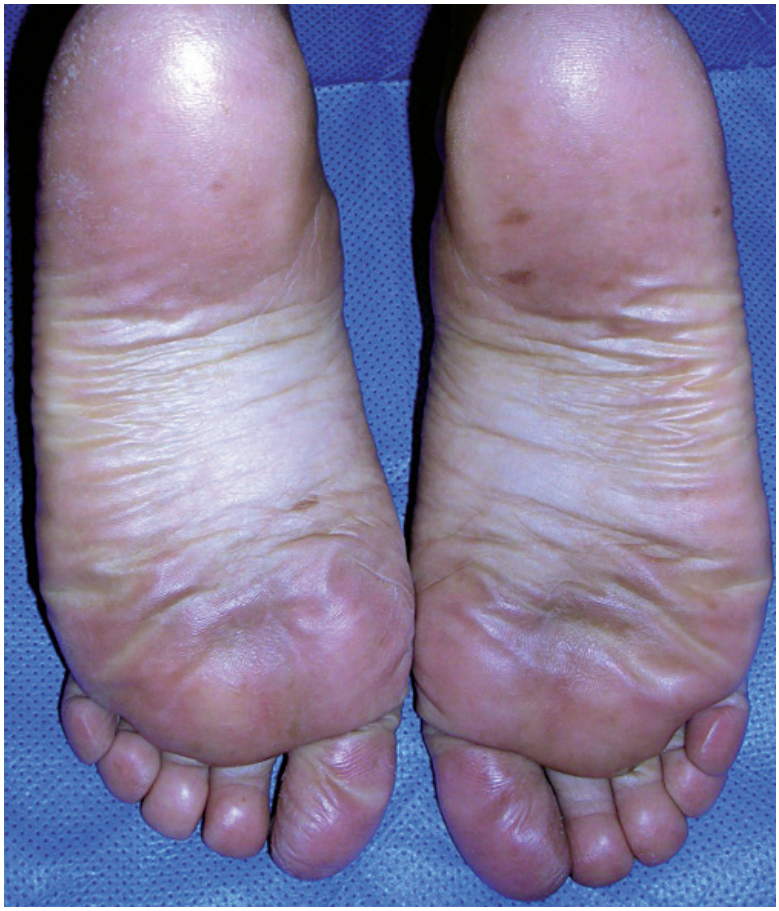

Figure 4. *Erythema, shedding, and lentigines on soles.*

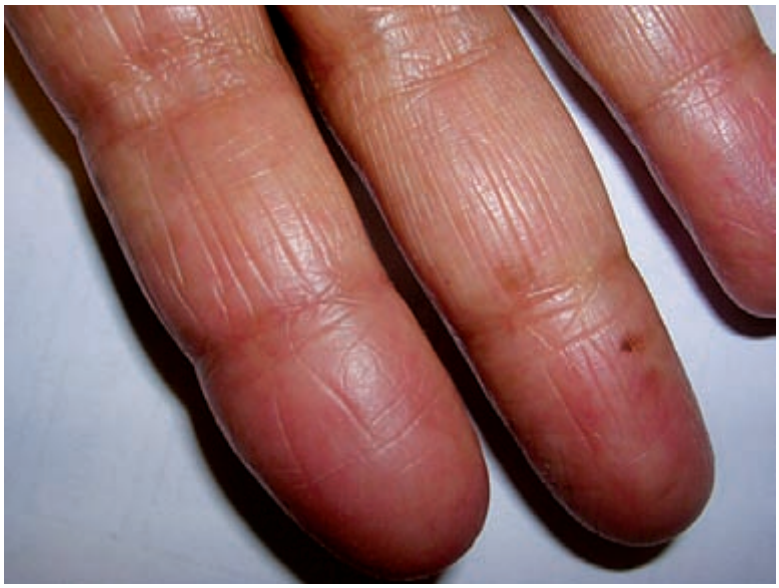

Figure 5. *Lentigines in various shades on hand.*

Xerosis (4 to 35 percent). More frequent with gefitinib. It begins after several weeks of treatment, and is more severe in elderly patients. It is associated with pruritus and fissures, and more pronounced on legs, hands, and feet. Occasionally there is vaginal or perineal dryness, and cutaneous fragility.[3]

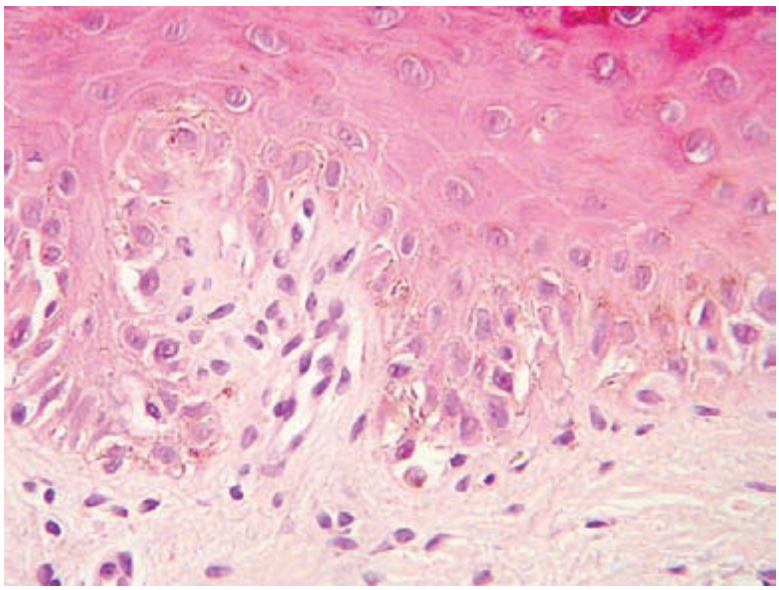

Figure 6. *Amount increase of melanocytes and basal pigmentation, in hand lentigines biopsy (H-E, 40x).*

Telangiectasia. They are found in patients with acneiform eruption and are dominant in face and trunk, giving a rosacea-like aspect.[20] They are self-involution and may be due to the production of angiogenic factors.[8]
Post-inflammatory hyperpigmentation, mainly in acneiform eruption sites. It is more frequent with gefitinib, enhances with photo-exposure and regresses gradually after chemotherapy has been completed.
Mucositis (2 to 36 percent), severity mild to moderate. It may be associated with aphthous ulcers in oral and/or genital mucosa.[16]
Other cutaneous adverse effects: petechiae and ecchymosis produced by leukoclastic vasculitis.[21] Urticaria, flushing, and anaphylactic reactions appear in less than 3 percent of patients (more common during infusion).

Treatment

Guidelines for acneifom reaction treatment have recently been published.[6]
Mild to moderate cases: minocycline or doxycycline 100 mg/day, with topic corticoids or calcineurin inhibitors. If no improvement occurs, duplication of antibiotic dosage is suggested.
Severe reactions: 200 mg/day with topics, and if no improvement is seen, addition of systemic corticoids is considered.
Grades 3 or 4: transient interruption of the drug, with posterior reintroduction in lower dosage; and in extreme cases, discontinuation and hospitalization in burn unit may be required.[8]
There are communications of success with numerous topic agents, such as: clindamycin, erythromycin, ketoconazole, econazole, low and intermediate potency corticoids, benzoyl peroxide, salicylic acid, metronidazole, vitamin D analogues and topic retinoids. Systemic treatments include erythromycin, lymecycline,[13] classic tetracyclines, fusidic acid and retinoids.[22] The use of local or systemic retinoids is not routinely advised, due to superposition of adverse effects.
In all cases, it is advisable to use emollients, photo-protectors, and oral antihistamines if pruritus appears.
Hydrocolloid, and propylene glycol dressings, or cyanoacrylate dressings are suggested for fissures. Adequate shoes, antiseptics, topic antibiotics and/or corticosteroids and administration of minociclyne or doxycycline 100 a 200 mg/day at least a month are recommended for paronychia.[2,15] Some cases require chemical or physical destruction of the pyogenic granuloma and partial avulsion of the nail plate.

5-Fluorouracil prodrugs

Main exponent is capecitabine, a fluoro-pyrimidine approved by FDA in 2001 for the treatment of metastatic breast and colorectal cancer in non-responding patients, or intolerant to standard chemotherapy.[23] It has also been used in advanced squamous-cell carcinoma.[24] It has the advantage of oral administration and a better safety profile, with less gastrointestinal and hematologic adverse effects than its metabolite. It is metabolized to 5-fluorouracil in three stages, and the last one takes place in the tumor tissue by thymidine-phosphorilase.[25]

Adverse effects

Hand-foot syndrome or erythrodysesthesia: Most frequent, and represents the limiting toxicity. Appearance is recorded between few days and one year after treatment begins (generally after the first or second cycle) and usually resolves spontaneously 1 or 2 weeks after it is finished.[26,27] It is dose-dependant, and most frequent and severe in women, elderly patients, or with peripheral vascular involvement.
It starts with dysesthesia (tingling, numbness, etc.) of palms and soles. In few days, erythema, edema, and desquamation appear. It may progress with pain, blisters, fissures, ulcers, and diverse extent of functional impairment. Presence of keratoderma and more severe syndrome has been described in black patients, as opposed to white patients.[23] Several classifications have been proposed to evaluate severity.[26] The most widely used are those from the World Health Organization (WHO) and from the National Cancer Institute (NCI) (**Table 2**).
Pathogenesis. Several theories have been proposed, such as an increase of the thymidine-phosphorilase enzyme levels in palm and sole keratinocytes, drug elimination through eccrine glands and intervention of local factors such as site vascularization, temperature, and pressure.[26]
Histopathology. Vasodilation, perivascular dominant lymphocyte inflammatory infiltrate, spongiosis, and lymphocyte exocytosis are found in the initial stages. In more advanced cases, basal vacuolar degeneration, focal presence of necrotic keratinocytes, and compact hyperkeratosis are seen.[23,26]
Treatment. Mild to moderate cases of hand-foot syndrome only require symptomatic treatment, consisting in avoiding the use of tight or too loose shoes, application of emollients, coldcompreses, and inter-

mediate to high potency topic corticosteroids may be used for short periods of time.
Some authors suggest the addition of hydroxyquinoline sulfate, amifostine, or urea to emollients. The use of patches of nicotine, vitamin E, pyridoxine, cyclooxygenase inhibitors (COX 2) is also described.[26]
In more severe cases, in addition to the measures mentioned above, adhesives with cyanoacrylate may also be used for fissures, and hydrocolloid dressings for ulceration. In grades 2 and 3, if support measures are insufficient, the drug may be discontinued until improvement is achieved, and then continue with a 25 to 50 percent reduced dosage. In grade 4, the treatment consist of the above treatment by 50% or definite interruption of the drug.[26]

Hyperpigmentation. It may be general or, more frequently, localized in palms and soles. It is a rare event (3-5 percent) and dominant in dark-skinned patients, Asians, or blacks.[23,25] Less frequently, pigmentation may be found in photo-exposed areas, on venous courses and striated melanonychia.[28] Etiology is not yet clear and it supposedly has a post inflammatory cause o direct stimulus of the drug or its metabolites upon melanogenesis.[28]
Eruptive lentiginosis. It is a rare phenomenon. It is described in relation to immunosuppression, either by AIDS, corticoid treatments, transplants, neoplasia, chemotherapy, or PUVA. Although common with the use of 5-fluorouracil, there are only two communications with prodrugs.[27,28] Dominant on palms and soles, the grounds for this preferential localization is unknown. Woodhouse et al.[29] suggest it may be due to local increased amount of MSH receptors, or to alteration of melanocyte proliferation regulatory factors.
Nail alterations: onycholysis, brittleness, discoloration, or striated melanonychia.
Inflammation of pre-existing actinic keratoses. Like 5-fluorouracil, a phenomenon ceasing when the cytostatic treatment is finished.[30]
Other adverse effects: eruptions in photo-exposed areas,[31] xerosis, radiation recall (inflammation of a previously irradiated area when a drug is taken), and vitiligo, alopecia, and mucositis.

Conclusion

With reference to IEGFRs, it is essential to take into account that acneiform eruption such as the one described in both of our patients, is a sign of good anti-tumor response, and the patient should be informed. In most cases, it is mild to moderate and improves with simple therapeutic interventions, reinforcing the non-discontinuation or reduction of dosage concept, unless severity so requires.
In the case of 5-fluorouracil prodrugs, severity of the hand-foot syndrome only required dosage reduction in one patient. The rest improved with only local measures. Likewise, we wish to highlight the need to recognize eruptive lentiginosis as one of its side effects, which although seldom communicated in the literature, was observed by us in the four patients receiving this drug. Acknowledgment of this effect allows us to inform the patient of its relation to the drug, understand its significance, and perform long-term follow up of these lesions.
It is imperative for the dermatologist to know side effects in detail, their implications, and treatment options of these new anti-neoplastic drugs, to improve the patient's quality of life without resignation of therapeutic efficacy.

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