Adverse mucocutaneous reactions to chemotherapeutic agents - Part I

Reações tegumentares adversas relacionadas aos agentes antineoplásicos – Parte I

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Abstract: The local and systemic treatment of tumors can cause changes in the skin, mucous membranes, hair and nails. Accurate diagnosis and appropriate treatment of side effects require knowledge about the patterns of the most common adverse reactions to drugs the patient may be using. The dermatologist must be familiar with the manifestations of certain soft tissue neoplasms, as well as with the adverse mucocutaneous forms of cancer treatment.
Keyword s: Chemotherapy, adjuvant; Drug therapy; Drug therapy, combination; Skin; Skin abnormalities; Skin pigmentation

Resumo: O tratamento local e sistêmico das neoplasias pode causar alterações na pele, membranas mucosas, cabelos e unhas. O diagnóstico preciso e o tratamento adequado destes efeitos colaterais requerem conhecimento dos padrões das reações adversas mais comuns para as medicações que o paciente está utilizando. O dermatologista deve estar familiarizado com as manifestações tegumentares das neoplasias, bem como com os efeitos adversos mucocutâneos dos tratamentos antineoplásicos.
Palavras-chave: Anormalidades da pele; Quimioterapia; Quimioterapia combinada; Membrana mucosa; Pele

INTRODUCTION

The skin, mucous membranes, annexes (sebaceous and sudoriparous glands) and the phaneros (hair and nails) are tissues with rapid cellular proliferation, and thus susceptible to adverse reactions (toxic or hypersensitive) resulting from systemic chemotherapeutic treatment. Antineoplastic agents are defined as substances that inhibit or prevent the proliferation of neoplasms. Due to their high metabolic rate, the skin, mucous membranes, and annexes are one of the most important target organs of the toxicity associated with chemotherapy. Reactions can present with disseminated exanthematous eruptions, non-specific, or distinct cutaneous lesions. Some drugs can trigger localized reactions due to extravasation to tissues adjacent to the areas of application. [1-4]

Exanthematous reactions, such as erythema multiforme, non-specific, are more common, and many of them are attributed to hypersensitivity

Approved by the Editorial Board and accepted for publication on 31.07.2009.
* Work conducted at the Cutaneous Oncology Laboratory, Division of Clinical Dermatology, Clinical Hospital, and at the Division of Clinical Oncology, "Octávio Frias de Oliveira" Cancer Institute of Sao Paulo – Sao Paulo, Brazil.
Conflict of interest: None.
Financial support: None.

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mechanisms. [4] Certain local toxicity, such as alopecia, mucositis, nail alterations or hand-foot syndrome, is more specific and less common, frequently associated with particular drugs or groups of drugs. [2]

The identification of the reaction pattern associated with the trigger drug and of the possible dose-limiting toxicity is of extreme importance to the assistant physician, as well as the differential diagnosis with infectious processes and specific manifestations of the neoplasm.

Most reactions can be reverted with dose reduction or with an increase of the interval between doses. Some toxic effets can be successfully treated or prevented. Medication administered before the chemotherapeutic treatment can prevent hypersensitivity reactions. The use of oral antiseptic solutions is useful in the control of mucositis.

Some dermatologic reactions to new antineoplastic agents, such as epidermal growth factor receptor inhibitors, have been associated with antitumoral efficacy.[1]

Other adverse effects may be mistaken for reactions to chemotherapeutic drugs and include infections resulting from immunosuppresion, paraneoplastic syndromes, graft/host disease (GVHD), nutritional deficiencies, development of skin malignancies, and metastatic primitive tumor. [2,3]

There are several classifications of reactions to antineoplastic drugs. The lack of a systematized multidisciplinary approach does not provide all the microscopic data and physiopathogenic mechanisms that originate the lesions. Therefore, the classification adopted didactically groups the eruptions based on the target cells and mechanism of action of the drugs (Chart 1).

1. Alterations of the phaneros and cutaneous annexes

1.1. Alopecia

Alopecia is the most common adverse skin manifestation of the chemotherapeutic treatment. There are two types of drug-induced alopecia: the anagen effluvium and the telogen effluvium. [5] In the anagen effluvium hair loss occurs due to the sudden interruption of the mitotic activity of the hair matrix, one to two weeks after the start of chemotherapy, leading to lack of hair production or its thinning (Pohl-Pinkus constrictions). [1-6] The weakening of the hair shaft in this context predisposes the hair to breakage and sheading during the act of combing. They involve the hair, eyebrows, beard, axillary and pubian hair. It is dose-dependent and reversible. New hairs often grow back with a different color and texture. In the telogen effluvium, hairs move prematurely to a resting phase with subsequent loss of normal hair.

The antineoplastic agents that most frequently cause the anagen effluvium lead to diffuse hair loss, of sudden onset, from 7 to 10 days after the start of chemotherapy. [5] Hair loss becomes more pronounced about 1 to 2 months after the start of treatment. Even though hair loss is intense, about 10% of the pilous follicles are usually in a resting phase at the time of the administration of the drug, and this determines incomplete hair loss. With repeated treatment cycles, alopecia totalis may occur. This type of effluvium is generally reversible when treatment is suspended and occasionally permanent with the use of ciclophosphamide and bussulfan. Hair grows around 1 cm per month, possibly showing new texture and color. The chemotherapeutic drugs more often associated with alopecia when used in isolation are represented in chart 2. The incidence described for combined regimens can be found in table 1.

Preventive measures to limit hair loss have had limited success. Hypothermia of the hair scalp or tourniquets applied in this region may reduce the perfusion of the drug in the pilous follicles and delay the start of or minimize hair loss. This procedure is contraindicated for patients with hematologic neoplasms such as leukemias, lymphomas, and other potentially metastatic tumors of the hair scalp. Topical minoxidil is not effective in the prevention of drug-induced alopecia, but it may shorten its duration. [7,8]

1.2. Trichomegaly and hair curling

Hair alterations with acceleration of growth and shaft changes are observed with the use epidermal growth factor receptor inhibitors (EGFR) (Figure 1). [9-12]

1.3. Ungueal, subungueal, and periungueal alterations

Nail alterations can present with a reduction of the nail growth speed, fragility, lines of discoloration (Mees' lines), transversal depressions (Beau's lines), hyperpigmentation, onycholysis with subungueal aseptic abcesses, photoonycholysis, paronychia, and pyogenic granulomas of the periungueal folds. Nearly all antineoplastic agents can lead to reduction of growth speed, nail fragility, Mees' lines and Beau's lines. [13-16] Hyperpigmentation can occur due to the use of cyclophosphamide, hydroxyurea, fluoropirimidines, such as 5-fluorouracil (5-FU) and specially anthracyclines like doxorubicin and daunorubicin (Figure 2). [17-19] Painful onycholycosis and subungueal abcesses are due to the use of taxanes (docetaxel/paclitaxel) and anthracyclines (doxorubicin). [20-22] Ingrown nails, paronychia, and pyogenic granuloma are associated with the use of tyrosine kinase inhibitors of the epidermal growth factor receptor (EGFR), such as erlotinib and gefitinib (Figure 3). [1] The fenestration or avul-

CHART 1: Adverse skin reactions associated with chemotherapeutic agents

1. Alterations of the phaneros and cutaneous annexes	1.1. Alopecia 1.2. Trichomegaly and curling of the scalp hair 1.3. Ungueal, subungueal and periungueal alterations 1.4. Neutrophilic eccrine hidradenitis 1.5. Eccrine squamous syringometaplasia 1.6. Acral erythema or palmoplantar erythrodysesthesia syndrome 1.7. Acneiform eruption
2. Mucous membrane alterations	2.1. Stomatitis
3. Epidermal, dermal and collagen alterations	3.1. Intertrigo 3.2. Hyperpigmentation 3.3. Autoimmune reactions 3.4. Inflammation of preexisting keratosis 3.5. Leg ulcer
4. Vascular alterations	4.1. Vasomotor alterations 4.2. Flushing
5. Interaction with radiation	5.1. Interaction with UV light 5.2. Radiation-induced memory reactions 5.3. Radiation exacerbation
6. Hypersensitivity reactions	6.1. Hypersensitivity reactions
7. Local reactions	7.1. Local toxicity 7.2. Drug extravasation
8. Diverse reactions	8.1. Periorbital edema 8.2. Lymphocyte recovery skin eruption 8.3. Skin toxicities associated with EGF/TKi anti-receptors 8.4. Other adverse skin reactions observed with chemotherapeutic agents

* EGFR/TKi: *epidermal growth factor receptor tyrosine kinase inhibitor*.

CHART 2: Isolated chemotherapeutic agents that most often cause alopecia

Complete Alopecia	Cyclophosphamide (high doses) Doxorubicin Docetaxel Dactinomycin Irinotecan Topotecan Bleomycin Paclitaxel
Incomplete Alopecia	Etoposide Ifosfamide Mitomycin C Fluorouracil Melphalan Mitoxantrone Gemcitabine Methotrexate Vinca alcaloids

sion of the lamina should be considered when abscesses that involve more than 50% of the nail bed are present. In these more severe cases, the temporary suspension of treatment, longer intervals between cycles, and dose reduction should be considered.

1.4. Neutrophilic eccrine hidradenitis

It is a rare, non-specific disease that often occurs when chemotherapeutic drugs are used in combination. This makes it difficult to know which drugs are responsible for causing the disease. Cytarabine is the most commonly cited drug; however, others are also implicated, such as bleomycin, chlorambucil, cyclophosphamide, cytarabine, doxorubicin, lomustine, mitoxantrone, busulfan, carmustine, cisplatin, cyclophosphamide, etoposide, 5-FU, methotrexate and thiotepa. Some authors consider neutrophilic eccrine hidradenitis (NEH) as a paraneoplastic phenomenon, since it has been found in an early case of acute myeloid leukemia, not yet treated. [1,23,24] It has

Table 1: Incidence of alopecia with combined regimens

Regimen	Incidence of Alopecia, %
CMF- Cyclophosphamide, Methotrexate, 5-FU	10
FAC- Cyclophosphamide, doxorubicin, 5-FU	40
EP- Cisplatin, Etoposide	90
MOPP/ABVD	68
Carboplatin, Paclitaxel	50 a 100
IFL- Irinotecan, Leucovorin, 5-FU	37

been associated with HIV infection, *Nocardia, Serratia, Enterobacter, Staphylococcus*, and with patients receiving granulocyte colony-stimulating factor (G-CSF).[1,25, 26] The mechanism is unknown, but it may be due to the excretion of the chemotherapeutic drug by the eccrine glands and its direct toxic effect on the eccrine epithelium.[25,26]

The clinical condition may be preceded by fever and unspecific clinical signs.[24,25] Skin eruptions are distributed in the head, neck, trunk, and extremities, with lesions that vary from erythema, papules, nodules, and pustules to papular plaques. Lesions may be purpuric or hyperchromic, single or multiple. They appear between 2 days and 3 weeks from the start of treatment, regressing spontaneously without scarring or sequelae 1 to 4 weeks after the suspension of the drug.[24-28]

The differential diagnosis is vast and includes: sepsis, septic embolism in a post-chemotherapeutic neutropenic patient, vasculitis, leukemia *cutis*, hypersensitivity reaction, urticaria, polymorphous erythema, and neutrophilic dermatoses such as Sweet's syndrome, bullous pyoderma gangrenosum and atypical pyoderma gangrenosum.[18,28,29] Due to the unspecific clinical presentation of the disease and the great number of differential diagnoses, some authors suggest that NEH be included in the diagnostic hypotheses of any eruption that may occur in patients undergoing chemotherapy, and its final diagnosis is established via histopathology. Therefore, histopathology is essential for conclusive diagnosis. It is constituted by a dense neutrophilic infiltrate, inside and around the eccrine glands, with necrosis of the eccrine epithelium cells. Involvement of the approcrine glands has been reported. Occasionally, squamous syringometaplasia, hemohrrage and edema of the dermis, spongiosis and/or vacuolization of the basal layer of the epidermis, necrosis of keratinocytes and mucine deposits inside and around the eccrine glands may occur. 30 In patients with severe neutropenia, the neutrophilic infiltrate may be absent; however, necrosis of the eccrine epithelium is typical.[31] NEH is a self-limiting adverse reaction.[31] Frequently, the process resolves within a month, without treatment. In other chemotherapy cycles, 60% of the patients may relapse. 24 The efficacy of the profilactic or therapeutic use of systemic corticosteroids, dapsone or non-hormonal antiinflammatories is still questionable.[32,33]

1.5. Eccrine squamous syringometaplasia

Eccrine squamous syringometaplasia is an unusual adverse reaction to chemotherapeutic drugs. It can also be found in association with chronic ulcerations, skin tumors, exposure to toxic agents and several inflammatory processes. Therefore, it is not a his-

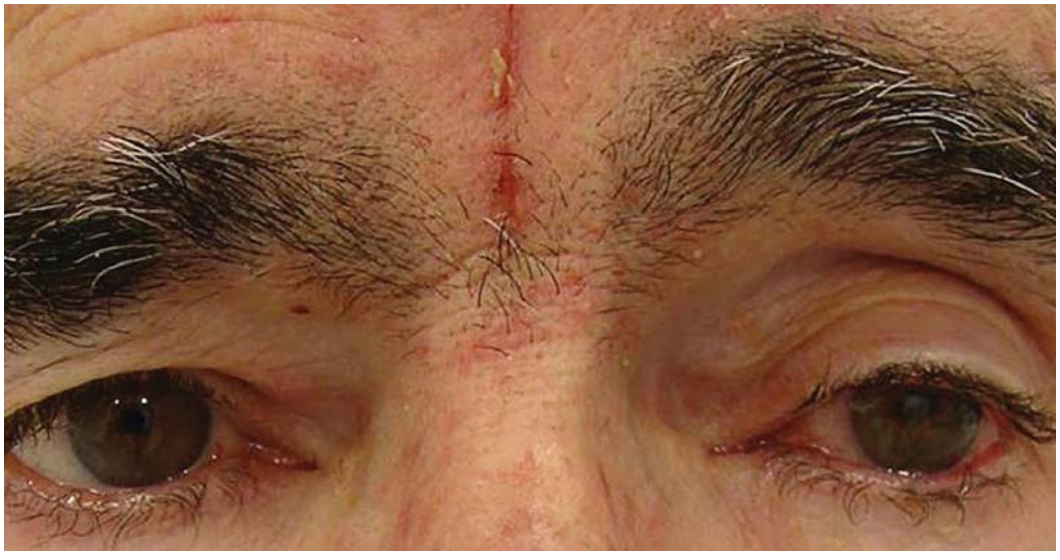

Figure 1: Excessive growth and increase of the eyebrow and eyelash curvature due to erlotinib. Trichomegaly and hair curling

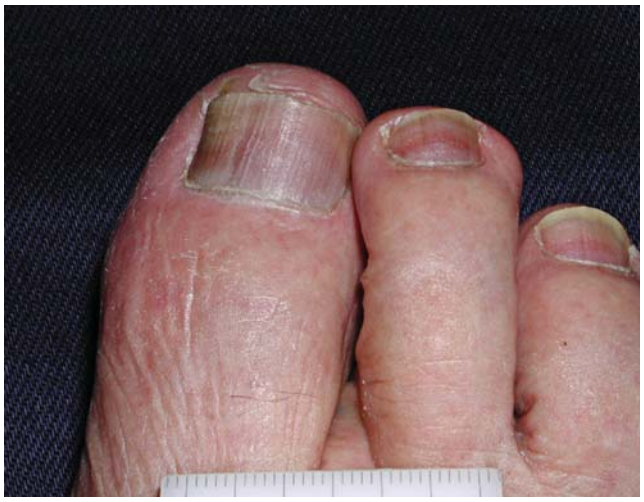

Figure 2: Nail hyperpigmentation due to bleomycin. Ungueal, subungueal and periungueal alterations

topathologic reaction exclusive to the use of chemotherapeutic drugs. The mechanism of neutrophilic eccrine hidradenitis is unknown, but it can be the result of the excretion of the drug by the eccrine glands and its direct toxic effect on the eccrine epithelium. It is postulated that eccrine squamous syringometaplasia represents the final non-inflammatory spectrum of adverse reactions to chemotherapeutic drugs in the eccrine glands. [1,34]

Similarly to neutrophilic eccrine hidradenitis, eccrine squamous syringometaplasia also has an unspecific clinical presentation, constituted by erythematous maculae, papules and papular plaques or vesicles, localized or disseminated. [35] Lesions develop between 2 to 39 days after the start of chemotherapy and improve spontaneously after 4 weeks. [36] The diagnosis is histopathological, characterized by the presence of squamous metaplasia of the eccrine glands in the papillary dermis. Minimal and focal necrosis of the eccrine gland epithelium, fibroblastic proliferation and edema of the periductal estroma may occur. [37] Contrary to NEH, the neutrophilic infiltrate is minimal or absent. Squamous eccrine syringometaplasia has been described as an accidental histological finding in other conditions not associated with chemotherapy. [38]

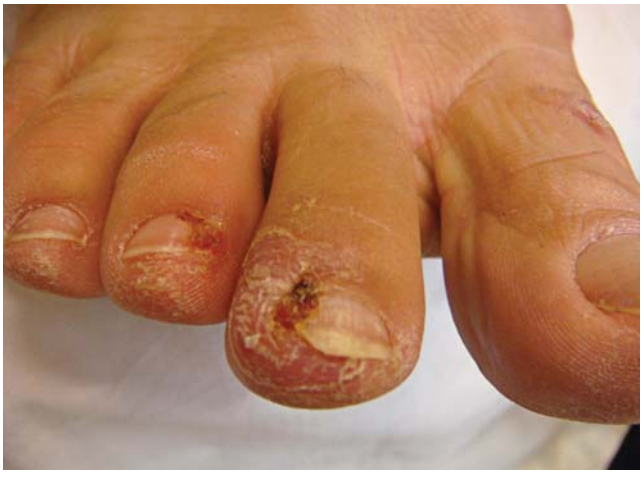

Figure 3: Pyogenic granulomas on the ungueal folds of the left foot after the use of erlotinib. Ungueal, subungueal and periungueal alterations

Eccrine squamous syringometaplasia does not appear to be associated with a specific chemotherapy agent or malignancy. Numerous drugs have been related such as cytarabine, mitoxantrone, daunorubicin, cisplatin, 5-fluorouracil, doxorubicin, cyclophosphamide, etoposide, methotrexate, busulfan, mephalan, and carmustine. Eccrine squamous syringometaplasia has been observed in association with palmoplantar erythrodysesthesia syndrome, in radiation-induced memory reactions and in patients who underwent bone marrow transplantation and received high doses of chemotherapeutic drugs. The condition often spontaneously resolves. [1,3,7,19]

1.6. Acral erythema or palmoplantar erythrodysesthesia syndrome

Described in 1974, it is also known as: Burgdorf's syndrome, palmoplantar erythema, hand-foot syndrome and toxic erythema of the palms and soles. 39,40 It occurs more frequently in patients treated with cytarabine and fluoropirimidines, especially capecitabine, which is the oral 5-FU pro-drug. After alopecia and mucositis, it is the most common adverse reaction to chemotherapy. Other agents less frequently associated with palmoplantar erythrodysesthesia syndrome are cisplatine, cyclophosphamide, citarabine, doxorubicin, daunorubicin, doxifluridine, etoposide, floxuridine, hydroxyurea, mercaptopurine, methotrexate, mitotane, paclitaxel, docetaxel and vinorelbine. [41,42]

It is estimated that this adverse reaction occurs with 6% to 64% of the patients treated with different chemotherapeutic regimens. Most patients show a prodome of dysesthesia, with a tingling (pins and needles) sensation on the palms and soles. Within a few days, the reaction evolves to a feeling of pain and burning with a well-demarcated edema and erythema. The erythema is symmetrical and sometimes more pronounced on the soft parts of the distal phalanges (Figure 4). [43] Hands are often more affected than feet. Some patients show light scaling with or without erythema. [44] A bullous variant has been described, representing a more severe form of the reaction, especifically associated with cytarabine and methotrexate (Figure 5). Lesions aggravate if the treatment is not suspended and the associated pain and edema may limit the movement of fingers. When the drug is suspended, the reaction progressively improves within

two weeks. [46] In some patients, when treatment is maintained despite the development of erythrodysesthesia syndrome, palmoplantar keratodermia may occur. [47] The reaction occurs more frequently in patients who undergo oral or continous infusional therapy with fluoropirimidines (2 to 18%), as compared with those submitted to bolus therapy (0.4 to 3%). 48 There are various classifications to measure the severity of palmoplantar erythrodysesthesia syndrome, but the two most commonly used are from the World Health Organization (WHO) and the *National Cancer Institute* (USA) (Chart 3). [48,49,50]

It is thought that in the pathogenesis of the process the local accumulation of the drug leads to degeneration with necrosis of the sweat glands, because its microscopic aspects are similar to those of eccrine squamous syringometaplasia and neutrophilic eccrine hidradenitis. [51] In the differential diagnosis the following should be considered: polymorphous erythema, erythromelagia, eccrine squamous syringomeplasia and neutrophilic eccrine hidradenitis. The most relevant differential diagnosis is acute graft vs. host disease (acute GVHD). The fundamental difference is that acute GVHD occurs in patients who have received a bone marrow transplant, in addition to extracutaneous involvement with gastrointestinal alterations (abdominal pain and diarrhea, elevation of hepatic enzymes). In cases of acute GVHD without extracutaneous manifestations, differentiation may be difficult. [52] Nevertheless, acute GVHD presents with diffuse erythema and can form papules, whereas palmoplantar erythrodysesthesia syndrome shows a well-demarcated erythema and edema. There are no relevant histopathological differences between them, except for necrosis of the satellite cell in all layers of the epidermis (apoptotic keratinocytes adjacent to lymphocytes) in acute GVHD and sometimes presence of squamous syringometaplasia in palmoplantar erythrodysesthesia syndrome. [50] The differentiation between these two disorders is essential because the use of cyclosporine is necessary to treat acute GVHD, but it worsens the patient's pain if used in the treatment of PPES. [40,53 50]

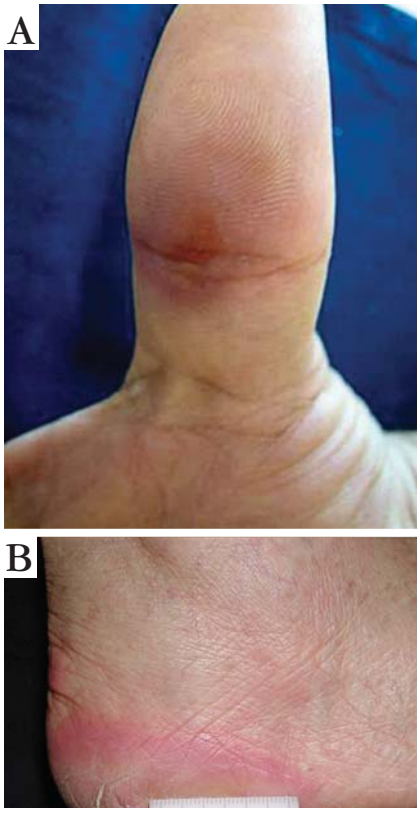

Figure 4: **A.** Erythematous violaceous plaque on the right index finger. **B.** Erythematous edematous plaque on the lateral and posterior face of the right foot. After the use of paclitaxel. Palmoplantar erythrodysesthesia syndrome

Apart from dose reduction, longer intervals between the cycles of chemotherapy and, as a last resort, the suspension of the drug, there is no specific treatment for palmoplantar erythrodysesthesia syndrome that has proved to be effective in a large series of cases. Some treatments have been suggested for small series of patients or case reports. General measures should be taken, such as reduction or suspension of the drug, longer intervals between chemotherapy cycles, dressings, elevation of the extremity, cold compresses, analgesic medication and emollients. [54] As a specific treatment, pyridoxine can be used if fluorouracil, liposomal doxorubicin, doxorubicin, docetaxel and etoposide have been administered; hand cooling (docetaxel); oral corticosteroids (doxorubicin, fluorouracil); strong topical corticosteroids (liposomal doxorubicin, cisplatin and fluorouracil), and topical DMSO at 99% (liposomal doxorubicin). Symptoms can be relieved with lesion care to prevent infection and elevation of the limb to reduce the edema. Cooling of hands and feet during treatment reduces the blood flow in these areas and may decrease the severity of the reaction. Strong topical corticosteroids have been used with mixed results when associated with emollients. Systemic corticosteroids are useful in some situations. Pyridoxine (vitamin B6) in doses of 200 to 300 mg/day can be useful to treat and prevent this reaction, except when cytarabine or vincristine are used. [36,55] Topical dimethyl sulphoxide (DMSO) at 99% four times a day for 14 days has cured some cases of palmoplantar erythrodysesthesia syndrome induced by pegylated liposomal doxorubicin. [56]

Toxic erythema caused by chemotherapeutic drugs

Some authors prefer to associate toxic erythema caused by chemotherapy with clinical lesions that present with painful erythema, with or without edema, often affecting the hands and feet, intertriginous areas such as the axillary and inguinal regions, and less frequently the elbows, knees and auricular pavillion. These eruptions may have a bullous compo-

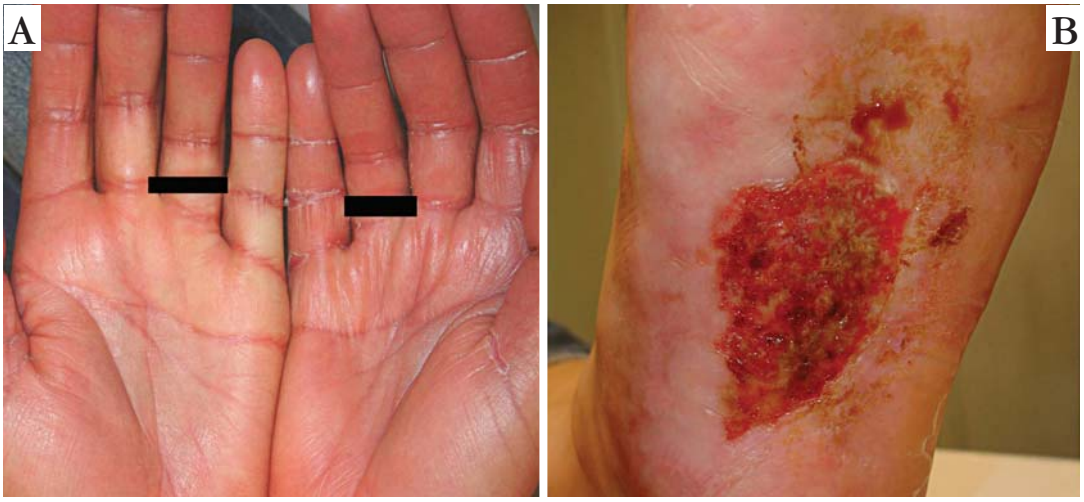

Figure 5: A. Palmar erythema and edema. **B.** Eroded lesion after rupture of a blister in the left sole, associated with edema and scaling. After the use of doxirubicin. Palmoplantar erythrodysesthesia syndrome

Chart 3: Levels of the Palmoplantar Erythrodysesthesia Syndrome

Criteria of the World Health Organization and Definition [48]	**Criteria of the National Cancer Institute and Definition** [49]
Level 1. Dysesthesia / paresthesia, tingling.	Level 1. Skin alterations or painless dermatitis.
Level 2. Discomfort in holding objects and strolling, erythema or edema.	Level 2. Painful skin alterations, without interfering with function.
Level 3. Painful erythema and edema of the palms and soles, periungueal erythema and edema.	Level 3. Painful skin alterations, interfering with function.
Level 4. Scaling, ulceration, blistering and severe pain.	–

nent, are self-limited and generally evolve with resolution and scaling associated with post-inflammatory hyperpigmentation. Many denominations used refer to histopathological findings or those given by various authors in different ocasions. Disorders like eccrine squamous syringometaplasia, neutrophilic eccrine hidradenitis, accral erythema and palmoplantar erythrodysesthesia syndrome would be, according to these authors, grouped under toxic erythema caused by chemotherapeutic drugs. The objective to group many disorders under the same denomination seeks to emphasize the superposition of clinical characteristics and promote an easy dialogue between medical specialties and with the patient. The clinical characteristics of the toxic erythema associated with chemotherapy are: (1) maculae or erythematous and/or edematous plaques on the hands and feet, intertriginous areas and less frequently on the elbows, knees and auricular pavillions, often appearing 2 to 3 days after the administration of the drug; (2) associated symptoms of pain (that may be disabilitating), burning, paresthesia, pruritus and/or hypersensitivity; (3) pale color, petechiae and/or sterile blisters, followed by erosion in areas of intense erythema; (4) scaling and spontaneous resolution without specific treatment, and (5) chance of relapse if an equal or higher dose is administered. Isolated papules may be found in the periphery of plaques. Papules and plaques may also be found in the head, cervical region, trunk and extremities. Onset of lesions after 2 to 10 months can be observed. The histological characteristics observed are atypia (larger cells and nuclei and nuclear pleomorphism), apoptosis of keratinoyctes, mitotic figures and bizarre mitotic configurations (astral mitosis), loss of polarity of the epidermal cells and apopstosis of keratinocytes, vacuolar degeneration of the basal layer of the epidermis, dermal edema and eccrine squamous syringometaplasia. Moreover, necrosis of the upper epidermis, similar to the alterations observed in pellagra, may also occur. The inflammatory infiltrates are usually minimal despite their abundant clinical profile. From these observations, it has been suggested that erythema is secondary and results from damage to keratinocytes leading to the release of cytokines and vasodilation.[57]

1.7. Acneiform eruption

It is the adverse effect more often associated with the use of epidermal growth factor receptor inhibitors (EGFR).[1] Onset happens one week after the

start of treatment with the EGFR inhibitor as a self-limiting eruption, dose-related, that affects the face, central region of the thorax, upper dorsum and more rarely limbs. It presents with follicular erythematous papules, pustules with or without comedones and scaling of the interfollicular skin (Figure 6).[58] Frequently, association with the following is observed: acral asteatosis, paronychia with pyogenic granuloma, oral and nasal aphthous ulcerations and hair alterations. Palms and soles are often free of lesions. Excessive follicular hyperkeratosis leading to the obstruction of the ostium with formation of a follicular corneal plug, rupture of the glandular wall, and consequent inflammatory process are suggested as pathogenic mechanisms.[59] In the histopathological exam a prominent corneal plug, with dilated infundibulum, with or without neutrophilic folliculitis, is observed. There is a positive correlation between the severity of the eruption and the tumoral response and survival. 59 We emphasize the need for attention to the eruption to improve the adherence to the chemotherapeutic treatment. The use of topical antiacne agents and oral tetracyclines improve the condition.[56] Topical emollients are indicated to treat xerosis.[59,60]

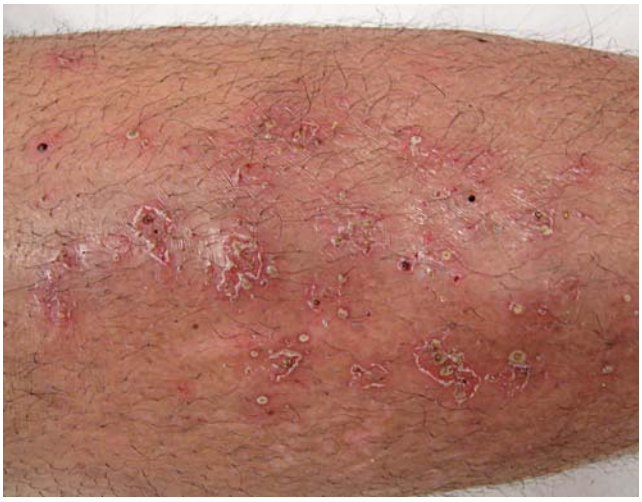

Figure 6: Multiple follicular pustules and interfollicular scaling on the anterior face of the leg after the use of erlotinib. Acneiform eruption

2.1. Mucous membrane alterations

2.1. Stomatitis

Oral mucositis is the main dose-limiting reaction of most chemotherapeutic drugs. About 40% of the patients being treated show some type of oral complication. These complications are often associated with drugs that affect the synthesis of DNA. The main causative agents are antimetabolic drugs and antitumoral antibiotics. The drugs more frequently associated with stomatitis are bleomycin, dactinomycin, methotrexate, topotecane, and fluorouracil. Unusually, the stomatitis caused by 5-fluorouracil is related to its continuous infusional administration or to the use of its oral prodrug, capecitabine, and is less frequently observed when 5-fluorouracil is administrated in bolus. The main mechanism is the direct toxicity of the drug, but it can result secondarily from the indirect effects of the drug on the bone marrow. In patients with head and neck tumors, cisplatin used during radiotherapy acts as a strong radiosensitizer. In these cases, there is more tumoral control but also greater severity of stomatitis due to a boost in the direct effect of radiotherapy.[61-63]

Since oral epithelium cells have a high mitotic index (renewal every 7 to 14 days), they become susceptible to the toxic effects of chemotherapeutic drugs. Moreover, there is atrophy of the oral mucosa, causing odynophagia, burning, xerostomia and mucous membrane ulcerations. Ulcerations may be initially focal and then become diffuse and confluent, with occasional vesicles and blisters. These alterations are more common in the non-keratinized mucosa and appear 4 to 7 days after the use of the drug. Resolution of lesions may occur after treatment is suspended, often within 3 to 4 weeks.[64]

Spontaneous or induced hemorrhage, especially gingival, may occur when platelet count is below 10,000/mm^3. Patients at a higher risk of developing stomatitis are those with hematologic neoplasms, those who are under 20 years old (high mitotic activity of the epithelium), patients with preexisting oral disease and poor mouth hygiene. Preventive measures include proper maintainence of oral hygiene by washing the mouth with water, saline solution, sodium bicarbonate or hydrogen peroxide. The use of cold water to prevent mucositis induced by fluorouracil and melphalan in high doses appears to be helpful. Other alternative clinical procedures, still not fully proven, consist in the use of chlorhexidine gluconate, betacarotene, and benzydamine chloridrate or sucralfate.[65,66]

Treatement is essentially of support with oral care, using agents such as magnesium or aluminum hydroxide and vitamin E. In addition, pain relief drugs like paracetamol and opioids (codein and morphine) may be necessary when the use of topical anesthesics such as benzocaine and lidocaine are not effective. Additional complications happen due to secondary bacterial, viral or fungal infections that may become systemic.[67, 68]

Palifermin, when used prophylactically, reduces the occurrence and duration of severe stomatitis in patients with hematologic tumors and submitted to bone marrow transplantation. Palifermin is a human recombinant factor of keratinocyte growth and protects various epithelial tissues. It acts not only on stomatitis, but also on mocusitis in general. A possible tumoral stimulating factor still limits its use in patients with epithelial tumors.[69, 70] ❑

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Como citar este artigo/*How to cite this article*: Sanches JA Jr, Brandt HRC, Moure EMD, Pereira GLS, Criado PR. Reações tegumentares adversas relacionadas aos agentes antineoplásicos - Parte I. An Bras Dermatol. 2010;85(4):425-37.