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ORIGINAL ARTICLES

Chemotherapy-Induced Acral Erythema: A Clinical and Histopathologic Study of 44 Cases

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Abstract. *Introduction.* Acral erythema, also known as palmoplantar erythrodysesthesia or hand-foot syndrome, is a relatively common cutaneous reaction caused by a variety of chemotherapeutic agents. It presents during cancer treatment as painful erythema and paresthesia affecting the palms and soles. It seems to be dose dependent and its appearance is determined by both the peak plasma concentration and the cumulative dose of the chemotherapeutic agent. The symptoms and histopathology findings are suggestive of direct cytotoxicity affecting the epidermis of the extremities caused by high concentrations of chemotherapeutic agents. The most commonly implicated agents are doxorubicin, 5-fluoracil and its derivatives, cytarabine, and docetaxel.

Material and methods. We present the clinical and histologic characteristics of a series of patients diagnosed with chemotherapy-induced acral erythema. The study included all patients who developed acral erythema lesions following chemotherapy between January 2000 and December 2003.

Results and conclusions. Out of 2186 patients who underwent chemotherapy, 44 cases of acral erythema were identified, representing an incidence of 2.01% during the study period and 16.75% of all cutaneous lesions attributed to chemotherapy. The most commonly implicated drug was 5-fluoracil administered by continuous infusion and the highest incidence was observed in patients treated with liposomal doxorubicin. Acral erythema was a dose-limiting toxic effect in 29.5% of cases. The histologic findings varied according to the clinical severity of the lesions and included interface dermatitis with variable keratinocyte necrosis, dilation of the superficial vascular plexus, and limited inflammatory infiltrate. The most commonly used treatment was pyridoxine, along with topical treatments such as cold compresses, emollients, and topical corticosteroids.

Key words: acral erythema, palmoplantar erythrodysesthesia, hand-foot syndrome, chemotherapy, adverse effects.

ERITEMA ACRAL INDUCIDO POR QUIMIOTERAPIA: ESTUDIO CLÍNICO E HISTOPATOLÓGICO DE 44 CASOS

Resumen. *Introducción.* El eritema acral (EA) es una reacción cutánea relativamente frecuente producida por diferentes agentes quimioterápicos. Otros términos con los que se le conoce son eritrodisestesia palmoplantar o síndrome pie-mano. Se presenta como un eritema doloroso en palmas y plantas asociado a parestesias en el contexto de un tratamiento oncológico. El EA parece ser dosis-dependiente, y tanto el pico plasmático como la dosis acumulada del quimioterápico determinan su aparición. La clínica y los hallazgos histopatológicos sugieren una citotoxicidad directa de la epidermis acral por las altas concentraciones de los quimioterápicos. Los agentes más frecuentemente implicados son doxorrubicina, 5-fluorouracilo y derivados, citarabina y docetaxel.

Material y métodos. Se presentan las características clínicas e histológicas de una serie de pacientes diagnosticados de eritema acral por quimioterápicos. Se incluyeron en el trabajo todos los pacientes sometidos a quimioterapia que desarrollaron lesiones de eritema acral durante un período de tiempo comprendido entre enero de 2000 y diciembre de 2003.

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Resultados y conclusión. Se encontraron 44 casos entre los 2.186 pacientes sometidos a quimioterapia, lo que supuso una incidencia del 2,01 % durante el período de estudio, y el 16,75 % de todas las lesiones cutáneas atribuidas a la quimioterapia. El fármaco más frecuentemente relacionado fue el 5-fluorouracilo en infusión continua, y la mayor incidencia se dio en pacientes tratados con doxorrubicina liposomial. El EA fue toxicidad limitante de dosis en el 29,5 % de los casos. Los hallazgos histológicos variaron según la intensidad clínica de las lesiones, encontrando una dermatitis de interfase con necrosis de queratinocitos variable, dilatación del plexo vascular superficial y un escaso infiltrado inflamatorio. El tratamiento más utilizado fue la piridoxina y las medidas locales como fomentos fríos, emolientes y corticoides tópicos.

Palabras clave: eritema acral, eritrodisestesia palmoplantar, síndrome pie-mano, quimioterapia, efectos adversos.

Introduction

Acral erythema, also known as hand–foot syndrome or palmar–plantar erythrodysesthesia, is a relatively common skin reaction caused by a variety of chemotherapeutic agents. The reaction is thought to be triggered by the direct cytotoxic action of the drug involved on the acral epidermis. Clinical signs and symptoms include painful erythema on the palms and soles, often accompanied by paresthesias. Symptoms tend to appear within 24 to 48 hours of chemotherapy initiation and resolve 2 weeks after completion. They reappear each time a new cycle is initiated.

Numerous reports of isolated cases and small series of patients with acral erythema have been published since the condition was first described by Zuehlke[1] in 1974 in a group of patients receiving mitotane for hypernephroma. Acral erythema has been reported to occur in as few as 6% and in as many as 64% of patients receiving chemotherapy, and the condition is often the reason for dose reduction or treatment interruption (dose-limiting toxicity).

In clinical practice, extent of involvement is normally categorized using either the grading system devised by the World Health Organization (WHO) or the common toxicity criteria (CTC) published by the National Cancer Institute (NCI). These systems are summarized in Table 1.

We present findings for a group of patients diagnosed with chemotherapy-induced acral erythema between January 2000 and December 2003 at the Instituto Valenciano de Oncología (IVO) in Valencia, Spain.

Materials and Methods

We performed a prospective study of a homogeneous group of patients receiving chemotherapy who developed lesions that were clinically consistent with acral erythema. The patients were consecutively enrolled through the dermatology department as they were seen in the department, the day hospital, or the hospital ward of the IVO. The combined study and follow-up period was 3 years (January 2000 through December 2003).

The study was conducted at the Fundación IVO, a specialized oncology center with 150 beds and the following departments: Medical Oncology, Radiotherapeutic

Table 1. Clinical Classification of Acral Erythema

WHO Scale		*NCI-CTC Scale*	
Grade	*Definition*	*Grade*	*Definition*
1	Dysesthesias/paresthesias, tingling in palms and soles	1	Skin changes without pain (erythema, peeling)
2	Discomfort holding objects and upon walking; erythema or painless swelling of palms and soles	2	Skin changes with pain, not interfering with function.
3	Painful edema and erythema; periungual erythema and swelling	3	Skin changes with pain, interfering with function
4	Peeling, blisters, ulceration; severe pain		

Abbreviations: CTC, common toxicity criteria; NCI, National Cancer Institute; WHO, World Health Organization.

Oncology, General Surgery, Gynecology, Urology, Otorhinolaryngology, and Dermatology. The institute also has a number of centralized services (laboratory, diagnostic radiology, nuclear medicine, and pathology). Because the IVO does not have a pediatric oncology unit, no children were included in the study. Based on data from the IVO's annual report in 2003, the hospital provided treatment to 21 936 patients in 2003, and of these, 4200 were new patients.

All the patients underwent a thorough clinical examination, including exploration of the skin, the oral and genital mucosa, and the hair and nails.

We ascertained which chemotherapy agents had been used and also noted the location and severity of lesions, the onset and duration of clinical signs and symptoms, and self-reported symptoms. A biopsy of the affected area was performed in several patients.

Results

Epidemiology

Of the 2186 patients who received chemotherapy during the study period, 44 cases of acral erythema were identified, representing a prevalence of 2.01% and 16.75% of all skin lesions attributed to chemotherapy.

The most commonly implicated drug was 5-fluorouracil, and the association was particularly strong when administered as a continuous infusion (22.7% of all cases of acral erythema). This was followed by 5-fluorouracil administered as a bolus injection (13.6%), docetaxel (13.6%), liposomal doxorubicin (11.3%), and vinorelbine (9%).

In terms of occurrence per treatment group, acral erythema was particularly common in patients treated with liposomal doxorubicin (41.6% of all the patients treated with this agent developed palm and sole lesions); this was followed by continuous infusion 5-fluorouracil (21.7%), cytarabine (11%), and gemcitabine (6.4%).

Table 2 provides a list of the different drugs associated with acral erythema in our series, together with a description of both the location and severity of the lesions according to the NCI-CTC.

Acral erythema displayed a statistically significant association with both liposomal doxorubicin and 5-fluorouracil administered as a continuous infusion. The corresponding *P* values for docetaxel, paclitaxel, gemcitabine, and cytarabine were close to statistical significance.

Clinical Signs and Symptoms

Clinical signs and symptoms included palmar–plantar erythema of varying severity, dysesthesias, and pain on pressure. Lesions appeared 5 to 7 days after initiation of treatment and lasted for 1 to 2 weeks. Repeated cycles of chemotherapy reactivated lesions—which were of increasing severity—in all the patients. Clinical manifestations and

Table 2. Cases of Acral Erythema in the Present Series

Drug	*Epidemiology*				*Severity*			*Site of Lesions*	
	No. of Patients	*%*	*Patients Receiving Treatment, No.*	*Occurrence, %*	*G1*[1]	*G2*[1]	*G3*[1]	*Palms/ soles*	*Palms/soles and elsewhere*
5-fluoracil CI	10	22.7	46	21.7	2	4	4	10	0
5-fluoracil bolus	6	13.6	786	0.7	1	4	1	6	0
Doxorubicin	3	6.8	649	0.4	0	2	1	3	0
L-doxorubicin	5	11.3	12	41.6	0	3	2	3	2
Paclitaxel	2	4.5	127	1.5	0	2	0	0	2
Docetaxel	6	13.6	156	3.2	0	3	3	5	1
Methotrexate	3	6.8	323	0.9	1	2	0	3	0
Vinorelbine	4	9	126	3.1	1	2	1	4	0
Gemcitabine	2	4.5	31	6.4	0	1	1	2	0
Cytarabine	1	2.2	9	11	0	1	0	1	0
Cyclophosphamide	2	4.5	991	0.2	2	0	0	2	0
Total	**44**				**7**	**24**	**13**	**37**	**5**

Abbreviations: CI, continuous infusion; G, grade; L, liposomal.
[1]Graded according to the National Cancer Institute Common Toxicity Criteria.

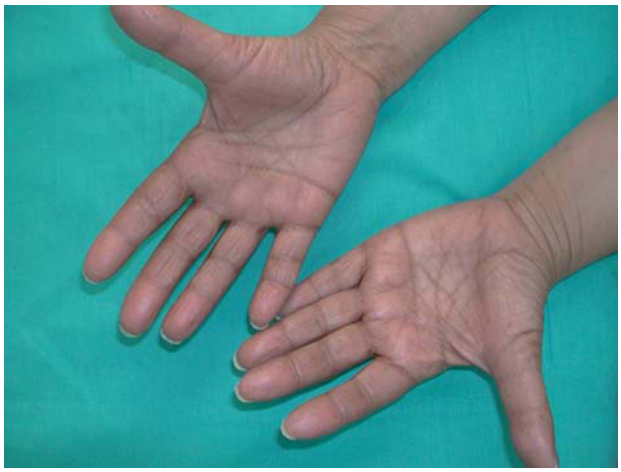

Figure 1. Grade 1 acral erythema. Erythema with no subjective discomfort.

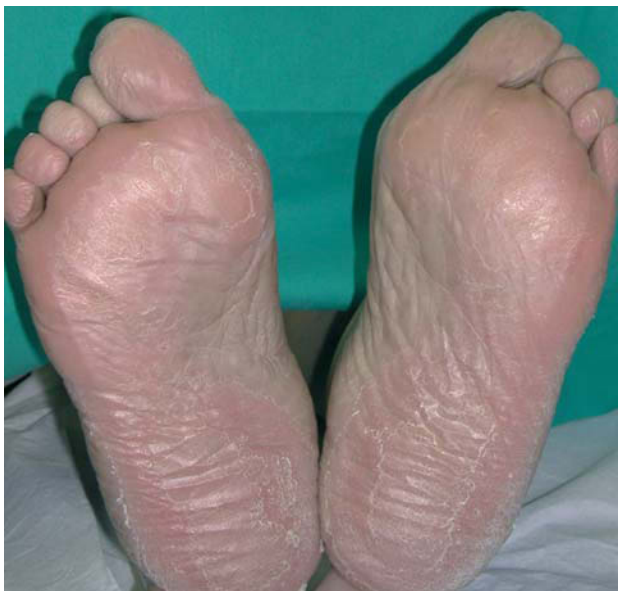

Figure 2. Grade 2 acral erythema. Erythema and fissures. Discomfort that does not interfere with activities of daily living.

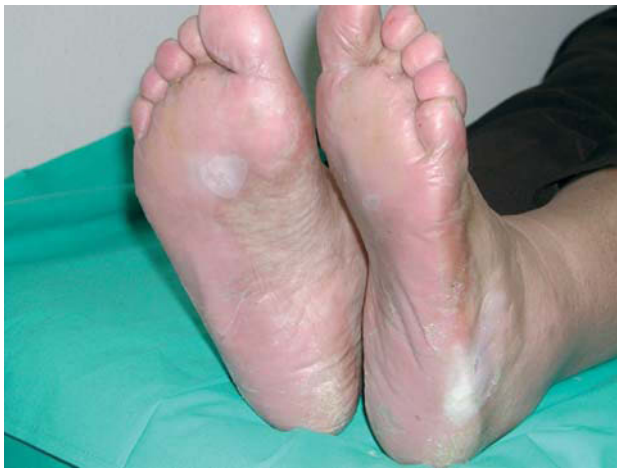

Figure 3. Grade 3 acral erythema. Erythema and blisters. Local discomfort that prevents activities of daily living.

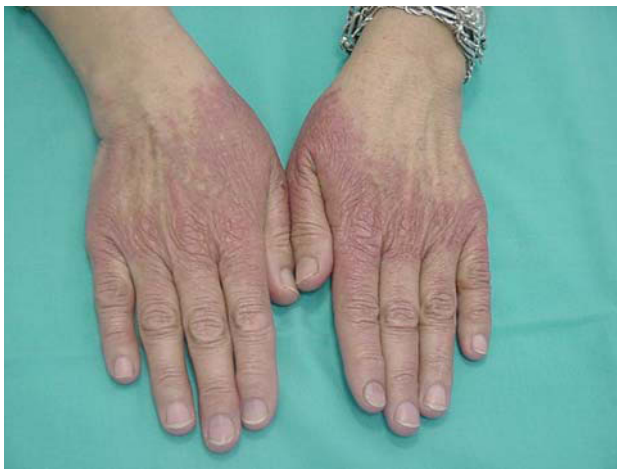

Figure 4. Lesions not confined to palms and soles. Involvement of back of fingers and hands.

extent of involvement were greatest in the final treatment cycles, suggesting cumulative toxicity.

We graded acral erythema severity using the NCI-CTC scale. This scale is primarily based on patient discomfort attributable to lesions but does not take account of clinical severity. We did, however, find discomfort and severity to be correlated. Patients with grade 1 or grade 2 toxicity, for example, only developed erythema and peeling, with very little edema or fissures (Figures 1 and 2), while those with grade 3 toxicity (n = 13) generally developed more severe palm and sole lesions, characterized by intense erythema, edema, peeling, and fissuring. Three of these patients—treated with docetaxel, liposomal doxorubicin, and gemcitabine—developed blistering lesions (Figure 3).

All the patients had palm lesions but not necessarily sole lesions. The former appeared earlier and were also more severe than the latter.

Five patients developed lesions in places other than on the palms and soles. These atypical lesions appeared on the backs of fingers and hands and on heels and ears (Figure 4), and were characterized by erythema, peeling, and pain on pressure in the affected area. Atypically located lesions occurred in patients treated with docetaxel, liposomal doxorubicin, and paclitaxel.

Acral erythema was a dose-limiting toxic effect in all the patients classified as grade 3 (n = 13, 29.5%).

Continuous 5-fluorouracil infusion, liposomal doxorubicin, and docetaxel were all significantly associated with dose-limiting acral erythema.

Tabla 3. Histologic Features of Acral Erythema

Type of Acral Erythema	*No. of Patients*	*Clinical Signs a nd Symptoms*	*Histology*
Grade [11]	2	Erythema and peeling	Dilated vessels in superficial vascular plexus Focal hydropic degeneration No inflammatory infiltrate Eccrine squamous syringometaplasia (n=1)
Grade [21]	3	Erythema, edema, fissuring	Vascular dilation Edema of the papillary dermis Focal hydropic degeneration Atypical nuclei in the basal layer Isolated necrotic keratinocytes Very slight inflammatory infiltrate Eccrine squamous syringometaplasia (n=1)
Grade [31] without blistering	3	Erythema, edema, fissuring, peeling	Interface dermatitis with few lymphocytes Hydropic degeneration of basal cells Edema of the papillary dermis Suprabasal clefting Keratinocyte necrosis Eccrine squamous syringometaplasia (n=1)
Grade [31] with blistering	2	Erythema, edema, blistering	Complete epidermal necrosis Reticular degeneration on superficial dermis
Back of hand	2	Erythema, scaling, isolated vesicles	Hydropic degeneration of basal cells Isolated keratinocyte necrosis Lichenoid inflammatory infiltrate

[1]Graded according to the National Cancer Institute Common Toxicity Criteria.

We also found a significant association between acral erythema and onycholysis in 5 patients (11.36%), all of whom had grade 2 and 3 lesions, triggered by doxorubicin (n = 1), docetaxel (n = 3), and bolus 5-fluorouracil (n = 1). Nail separation was severe in all of the patients and was considered an additional factor in defining acral erythema as a dose-limiting toxicity.

Histology

Biopsies of chemotherapy-induced lesions were performed in 12 patients and the corresponding histology findings are shown in Table 3.

The findings were similar to those described for chemotherapy-induced epidermal cytotoxicity: interface dermatitis with varying degrees of keratinocyte necrosis, abnormal maturation of basal keratinocytes, and frequent occurrence of eccrine squamous syringometaplasia. Our findings for acral erythema differed from other cytotoxicity findings, however, in that there was little or no inflammatory infiltrate.

Clinical severity was correlated with histopathologic findings in our series. While grade 1 patients only had dilated vessels in the superficial vascular plexus and focal involvement of the basal layer (Figure 5), grade 2 patients had dilated vessels in the superficial vascular plexus, papillary dermal edema, interface dermatitis with hydropic degeneration of basal cells, and isolated necrotic keratinocytes (Figure 6). Finally, patients with grade 3 toxicity had abundant keratinocyte necrosis, severe edema, epidermal detachment, and interface dermatitis. Histology findings for patients with blistering lesions included complete necrosis of the epidermis and reticular degeneration of the papillary dermis (Figure 7).

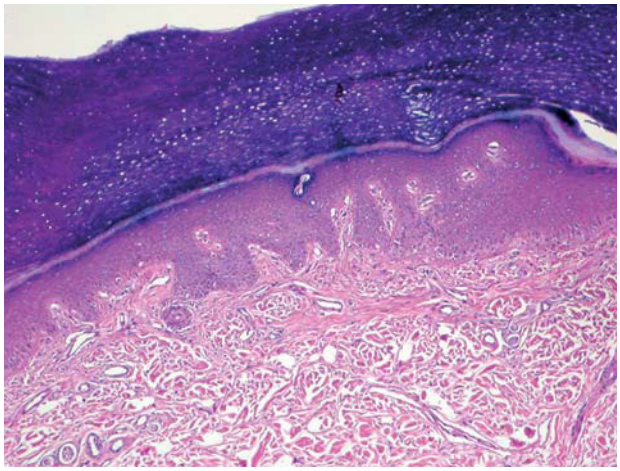

Figure 5. Grade 1 acral erythema. Dilated vascular plexus in papillary dermis, focal hydropic degeneration, and isolated necrotic keratinocytes. Hematoxylin–eosin, original magnification ×40.

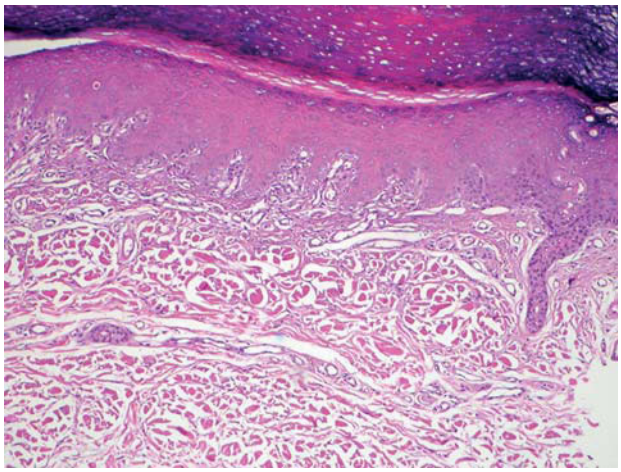

Figure 6. Grade 2 acral erythema. Dilated vascular plexus in papillary dermis and greater degree of keratinocyte necrosis. Hematoxylin–eosin, original magnification ×40.

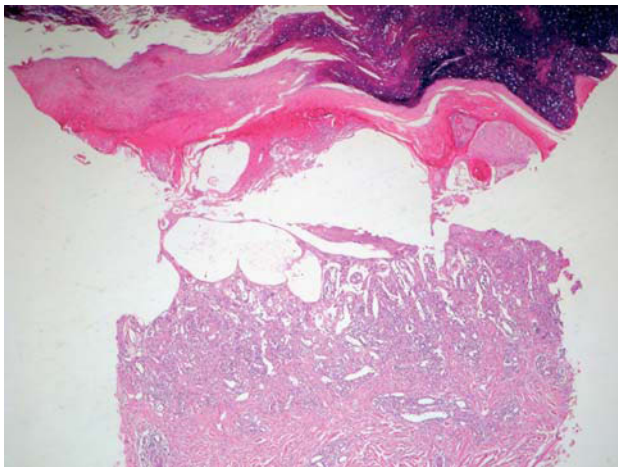

Figure 7. Grade 3 acral erythema. Subepidermal blistering. Necrosis due to epidermal coagulation and extensive vascular dilation. Hematoxylin–eosin, original magnification ¥10.

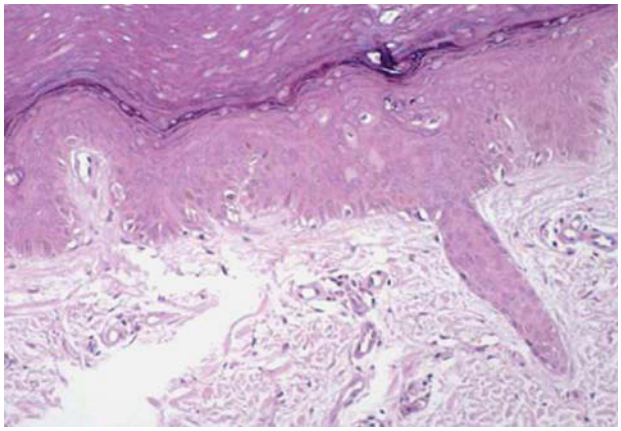

Figure 8. Eccrine squamous syringometaplasia and keratinocyte necrosis. Hematoxylin–eosin, original magnification ×100.

We found eccrine squamous syringometaplasia in 3 patients (25% of those who underwent a biopsy); these patients had grade 1, 2, and 3 acral erythema (Figure 8).

Discussion

Studies involving small series of patients have reported chemotherapy as the cause of acral erythema in as few as 6% and in as many as 64% of patients, and the reaction is classified as mild (grades 1 and 2) in almost 80% of cases.[2-6] In our series, 2.01% of the patients studied (44/2186) developed acral erythema, and this was the fourth most common chemotherapy-induced adverse skin reaction, after alopecia, mucositis, and hyperpigmentation.

Practically every chemotherapeutic agent has been found to be associated with acral erythema (in either isolated cases or small series of patients), and it is sometimes difficult to assess the true effect of a particular agent because combination therapies are now widely used. The most commonly implicated chemotherapeutic agents are 5-fluorouracil and its derivatives, doxorubicin, cytarabine, docetaxel, and methotrexate.

Acral erythema can affect up to 34% of patients receiving continuous 5-fluorouracil infusion and 13% of those receiving bolus 5-fluorouracil.[4,7-9] In our series, continuous 5-fluorouracil infusion (received by 22.7% of patients who developed acral erythema) was the most common cause of acral erythema; 21.7% of those who received 5-fluorouracil by continuous infusion developed the condition. The rate of occurrence of acral erythema is similar for continuous 5-fluorouracil infusion and capecitabine, an oral prodrug of 5-fluorouracil.[10-12] Capecitabine, however, is now one of the leading causes of acral erythema as it is more widely used than 5-fluorouracil.

Doxorubicin, another widely used chemotherapeutic agent, and one that is particularly popular in combination regimens, has also been associated with acral erythema.[13-15] Liposomal doxorubicin is a pegylated liposomal formulation of doxorubicin that is associated with lower hematologic and cardiac toxicity and a lower occurrence of alopecia. However, it is a common cause of skin toxicity (and acral erythema in particular), which occurs in 40% of patients treated with the drug.[16-22] The corresponding percentage in our series was 41.6%, higher than that of any of the other drugs studied. Liposomal doxorubicin is currently in widespread use to treat breast and ovarian cancer and sarcomas.

Cytarabine has also been strongly associated with acral erythema, particularly in patients who develop blisters.[23-26] We were unable to confirm this association, however, because the only patient who developed cytarabine-induced acral erythema in our series did not have blisters.

Acral erythema follows a practically identical clinical course in all patients, whatever the causative agent. It is characterized by the appearance of erythema, swelling, and possibly even blistering of the palms and soles, accompanied by paresthesias, pain, and burning. Symptoms typically start 48 hours after chemotherapy administration and most patients experience localized discomfort before the skin lesions appear. Soles tend to be less severely affected than palms, and lesions are often more evident on the fleshy parts and pressure areas. Lesions last for 1 to 2 weeks and get increasingly worse with additional cycles, and symptoms disappear following dose reduction or interruption of treatment.[27]

Acral erythema severity can be graded using different classification systems. The 2 most common systems used in clinical practice are the WHO and NCI scales (summarized in Table 1). While the WHO system measures clinical severity, the NCI system (used in the present study) measures the level of discomfort experienced by patients. Level of discomfort generally correlates with the clinical appearance of lesions (in our study also), suggesting that there is a good level of agreement between both grading systems.

Acral erythema may appear in atypical areas such as the dorsum of the hands and feet, heels and elbows, and even the ears,[28] face,[29] and genital areas.[30] Distal phalangeal necrosis has been described as a severe manifestation of acral erythema induced by liposomal doxorubicin.[22] Five (11.36%) of the patients in our series had lesions that predominantly affected the heels and the backs of hands and feet. The chemotherapeutic agents that had been used in these cases were liposomal doxorubicin (n = 2), paclitaxel (n = 2), and docetaxel (n = 1). Although, to the best of our knowledge, the association between acral erythema and these 3 agents has not been previously described, in our review of the literature, we found reports of lesions induced by both taxanes and liposomal doxorubicin that were very similar to those described in our patients.[31-33]

Five of the patients in our series developed onycholysis. The association between onycholysis and acral erythema was statistically significant, and particularly strong in patients with grade 3 toxicity. Onycholysis was most common in patients with severe acral erythema; the majority of these patients had been treated with docetaxel and many of them also had periungual lesions.

Acral erythema is a major dose-limiting effect of chemotherapy. In our series, it was responsible for dose reduction or drug withdrawal in 29.5% of patients. Continuous 5-fluorouracil infusion, docetaxel, and liposomal doxorubicin were associated most strongly with the more severe forms of acral erythema in our series. Acral erythema is the most common chemotherapy-induced dose-limiting toxic skin reaction. Indeed, it is the most serious dose-limiting effect of treatments involving liposomal doxorubicin and oral capecitabine.

The exact pathogenic mechanisms involved in chemotherapy-induced acral erythema are unknown. Because of its clinical and histologic similarities with graft-versus-host disease, it was initially considered to be an autoimmune disease in which chemotherapeutic agents induced changes in cell-surface receptors, triggering an autoimmune reaction.[34] Now, however, the most likely and widely accepted hypothesis is that chemotherapeutic agents have a direct adverse effect on epidermal cells. This hypothesis rests on the relationship between dose and lesion severity[18,35,36] and histopathologic similarities with other conditions caused by direct epidermal cytotoxicity.[37]

In the present study, we found several lines of evidence to support the hypothesis of a direct cytotoxic mechanism:

1. There was a correlation between lesion severity and dose (both peak plasma drug concentration during each treatment cycle and total cumulative dose).
2. Symptoms invariably improved or resolved following dose reduction or interruption of treatment in more serious cases.
3. Histology findings were similar to those reported for other direct cytotoxic reactions.
4. The association between acral erythema and onycholysis (a typical lesion in direct cytotoxicity) was statistically significant.

There are no clear explanations as to why this reaction is typically confined to the palms and soles, although it is probably related to certain physical factors that distinguish these areas from other parts of the body: thick stratum corneum, characteristic temperature gradient and vascular anatomy, rapid cell turnover, absence of sebaceous glands, abundance of eccrine glands, and wide dermal papillae. One hypothesis is that the excretion of the chemotherapeutic agent in sweat may favor a special immune response in the eccrine glands. One study suggested that anomalous expression of intracellular adhesion molecule-1 in the eccrine apparatus might favor the presence of natural killer cells, leading to direct cytotoxicity.[38]

While no studies have systematically reported histopathologic findings for acral erythema in large series of patients, there are many reports of isolated cases and small series that describe findings similar to those observed in other cases of direct chemotherapy-induced epidermal cytotoxicity.[5,20,39-48] These cytotoxic reactions are characterized by an interface dermatitis, a very slight infiltrate, and a varying degree of epidermal necrosis.[37] A review of the literature reveals that histopathologic changes in the epidermis include hydropic degeneration of the basement membrane, necrosis in isolated basal keratinocytes, and relative atrophy of the stratum spinosum. Occasional findings include abnormal maturation of keratinocytes, nuclear aberrations, atypical mitosis, and multinucleated

Table 4. Treatment of Acral Erythema

General Treatment	*Specific Treatment*
Dose reduction, lengthening of administration interval, drug withdrawal	Pyridoxine hydrochloride (5-fluoracil, doxorubicin, liposomal doxorubicin, docetaxel, etoposide)
Limb elevation	Cooling of hands and feet (docetaxel, liposomal doxorubicin)
Cold compresses	Oral corticosteroids (5-fluoracil, liposomal doxorubicin, methotrexate)
Avoidance of excessive manual work and walking	Oral corticosteroids (5-fluoracil, liposomal doxorubicin, cisplatin, docetaxel)
Emollients	topical dimethyl-sulfoxide, 99% (liposomal doxorubicin)
Topical antibiotics	Vitamin E (capecitabine, docetaxel)
Analgesics	

cells. Histopathologic changes in the dermis include vascular dilation, papillary dermal edema, and a very slight infiltrate in the dermoepidermal junction. Other remarkable findings include eccrine gland alterations in the form of eccrine squamous syringometaplasia.[5,38,42,48-50] In our series, we were able to match histologic manifestations of acral erythema to clinical severity. Mild reactions (grades 1 and 2 on the WHO and NCI scales), for example, were characterized by isolated keratinocyte necrosis in the basal cell layer and the appearance of atypical nuclei. More severe reactions (grades 3 and 4 on the WHO scale and grade 3 on the NCI scale), in contrast, were characterized by complete destruction of the epidermal basal layer, the presence of vesicles, and in some cases, complete necrosis of the epidermis.

Histologically, the main disorder that should be considered in the differential diagnosis of acral erythema is graft-versus-host disease.[34] The 2 entities are clinically similar and may occur simultaneously, making diagnosis complicated. Graft-versus-host disease, however, has several distinctive characteristics. In addition to the fact that it appears in patients who have undergone an allogeneic bone marrow transplant, the skin reaction typically starts on the face and upper chest area and can affect multiple areas of the body; the disease follows an aggressive course and there may also be internal involvement.[51]

Dose reduction, lengthening of administration intervals, and drug withdrawal are the only measures that have proven successful on a regular basis for treatment of acral erythema.

Several other methods have been proposed by authors reporting isolated cases and small series (Table 4), but their efficacy needs to be evaluated in prospective, randomized, controlled studies.[11]

Symptomatic relief can be achieved through wound care to prevent infection and limb elevation to reduce swelling, and also through the use of cold compresses, emollients, topical antibiotics, and analgesics.[11,28,52] The cooling of hands and feet during chemotherapy administration has been relatively successful in preventing docetaxel-induced acral erythema[53] and it may also reduce the severity and frequency of liposomal doxorubicin-induced acral erythema.[21] It also appears advisable to avoid heavy manual work, excessive walking, and exposure to localized heat.

Powerful topical corticosteroids have been used with varying levels of success, and the best results have been seen when used in conjunction with cold compresses and emollients. [16,29,54-57]

Systemic corticosteroids have been successfully used to treat and prevent acral erythema induced by 5-fluorouracil, liposomal doxorubicin, bleomycin, and methotrexate. Examples of corticosteroid use include prednisone (1 mg/kg/d),[56,58] dexamethasone (8 mg/12 h),[17] betamethasone (1.5 mg/d),[49] and intravenous methylprednisolone (1 mg/kg/d)[51] for 1 to 4 days after chemotherapy administration.

Pyridoxine hydrochloride (vitamin B_6) appears to be the most successful treatment. In our case series, it allowed us to continue chemotherapy administration in many patients without having to reduce the dose. Doses of between 300 mg and 500 mg per day have prevented the onset of acral erythema following treatment with 5-fluorouracil, docetaxel, etoposide, and doxorubicin.[8,35,57,59,60] It has also been shown in a canine model that pyridoxine hydrochloride delayed the onset of acral erythema and reduced its severity during chemotherapy with liposomal doxorubicin.[61] How this vitamin actually works is unknown but it has been suggested that it might regenerate injured nerve fibers.[62]

Topical dimethyl sulfoxide, 99%, applied 4 times a day over a period of 14 days has also been proposed as a treatment for liposomal doxorubicin-induced acral erythema.[63]

Finally, in one recent study, vitamin E treatment in a small group of patients with acral erythema due to combined capecitabine–docetaxel therapy improved

symptoms in all cases and allowed interruption of treatment to be avoided.[12]

Conflicts of Interest

The authors declare no conflicts of interest.

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