Clinics in Dermatology (2017) **35**, 55–63

ELSEVIER

Clinics in Dermatology

Acral manifestations of systemic diseases: Drug-induced and infectious diseases

Stefano Caccavale, MD*, Eleonora Ruocco, MD, PhD

Department of Dermatology, Second University of Naples, Naples, Italy

Abstract Drug reactions and systemic diseases often involve the skin. In particular, most drug-induced reactions and many infectious diseases present with dermatologic manifestations localized acrally, that is on distal portions of limbs (hand, foot) and head (ears, nose). A detailed review of all acral dermatologic signs of drug reactions and systemic diseases is beyond the scope of this paper, although some of these disorders will be discussed specifically here.

Acral manifestations of systemic diseases: drug induced

Purple glove syndrome

Phenytoin has been used for the treatment of seizures since 1956. It is administered intravenously in emergency departments and hospitals to patients with isolated seizures or undergoing neurosurgical procedures, who are unable to receive oral medication.[1] Although the cutaneous adverse manifestations of intravenous phenytoin administration were individually described[2,3] in 1984, it was in 1992 that the features were likened to and named "purple glove syndrome" (PGS) by Hanna.[4]

PGS is an infrequent but dreaded complication of intravenous phenytoin administration that may present with purple discoloration and painful swelling of the involved limb like a glove. In a prospective study,[1] the incidence of PGS among patients examined after intravenous administration of phenytoin was 1.7%; however, the incidence of PGS varies throughout the literature from 1.7% to 5.9% of phenytoin injections.[5]

The exact pathophysiologic mechanism of PGS is uncertain, but several theories exist to explain tissue injury and include extravasation injury or thrombotic event. The most obvious possible cause of phenytoin extravasation is line malfunction secondary to a variety of factors, such as dislocation of the intravenous access to the venous system, ruptured vessel during line placement, or improperly placed intravenous lines; however, PGS also occurs in cases where the line is properly placed and without any line dislocation preceding the symptoms of PGS.[6] To complicate the speculation on the etiology even more, there are reports of cases of PGS occurring after oral administration of phenytoin.[7] One theory points to phenytoin's lack of solubility that can result in precipitation after contact with patient blood. This precipitation may cause obstruction and lead to leakage of the drug into the soft tissue, or cause vessel damage leading to vasoconstriction and necrosis. Another theory involves the pH of the phenytoin, which has a weakly acidic pH. Its formulation is soluble only at high pHs and is not soluble in water. Sodium hydroxide is added to the solution for this reason; furthermore, propylene glycol and ethanol can also be added to increase solubility. The alkaline solution may stimulate vasoconstriction and vessel thrombosis as well as allow leakage into interstitial space by breaking down of endothelial cell junctions.[8] Regardless of how the soft tissue is exposed to the drug, phenytoin is protein-bound and thereby increases interstitial oncotic pressure, resulting in further irritation and edema of tissues.[6]

* Corresponding author. Tel.: +39-333-63-65-526.
E-mail address: stefano85med@libero.it (S. Caccavale).

http://dx.doi.org/10.1016/j.clindermatol.2016.09.008
0738-081X/

The progression of PGS tissue damage includes three stages. At first, the characteristic bluish-purple skin changes occur at the intravenous site within 2 to 12 h after administration. In the second stage, between 12 and 24 h postinfusion, the discoloration extends peripherally around all sides of the fingers, hand, and forearm; edema with or without skin blistering, sloughing, and possible ulceration may develop. Thirdly, signs of PGS usually resolve (within weeks to months), with the discoloration receding, starting from the outer edges and moving toward the original site of injury. Rarely, PGS may progress to necrosis, ischemia, vascular compression, or compartment syndrome. Recognition of PGS and initiation of appropriate treatment via immediate phenytoin cessation may minimize soft tissue damage and possible debilitating sequelae.[6]

The differential diagnosis of PGS includes cellulitis, necrotizing fasciitis, intravenous line malfunction and drug toxicity, arterial occlusion, venous thrombus, thrombophlebitis, Raynaud phenomenon, Buerger disease, and polyarteritis nodosa.

Initial supportive treatment includes immediate stop of phenytoin infusion, pain management, elevation of the affected limb, compression, massage, and gentle heating. These early conservative treatment measures prevent the development of serious necrosis. Intradermal hyaluronidase, topical nitroglycerin, and brachial plexus block have also been attempted with moderate degrees of success in combination with conservative therapies.[5] Severe PGS may need fasciotomy, skin grafts, or amputation.[9] Administration of a correct dose of the drug (15 to 20 mg/kg body weight) at a rate of lower than 20 mg/min (slow infusion rate) via a large cannula (20 gauge or larger) sited in a large-caliber vein (ie, not in distal extremities like the small veins on the back of the hand) has been associated with a lower occurrence of PGS. Dilution of phenytoin in normal saline (to achieve a concentration of 6.7 mg/mL) drastically reduces the occurrence of phlebitis, which in turn reduces the frequency of PGS.[5] It has been suggested that the use of fosphenytoin, the prodrug of phenytoin, should be preferred in patients at particularly high risk for PGS, because it is less toxic than phenytoin, less painful upon extravasation, less alkaline, and itself soluble without propylene glycol.[5]

Because of the widespread use of phenytoin, students of health sciences, practitioners, and nurses should be taught on this entity, and trained to administer phenytoin carefully to prevent this event.

Reactions to chemotherapeutic agents

Chemotherapeutic agents can give rise to numerous well-described mucocutaneous side effects, sometimes affecting exclusively or also acral body areas (Table 1).[10–14] In most cases, cutaneous reactions are not reasons enough to stop potentially life-saving treatments; however, identification of these reactions is important for both dermatologists and oncologists so that appropriate management and uninterrupted chemotherapy may be provided to patients with cancer.

- **Acral erythema (hand-foot syndrome [HFS] or acral erythrodysesthesia).** Several drugs may induce erythema, swelling, and pain of the digits. HFS is a symmetric, well-demarcated palmoplantar erythema that can blister and ulcerate. The pathogenic mechanisms are unclear. The most likely agents to cause HFS are 5-fluorouracil and cytarabine, as well as doxorubicin, hydroxyurea, methotrexate, mercaptopurine, cyclophosphamide, docetaxel, and mitotane. The hands are more extensively involved than the feet. The reaction starts 1 to 14 days after treatment and lasts for 1 to 2 weeks. The effect is dose related and tends to recur with each cycle of therapy but is harmless. The infiltrated plaques resolve spontaneously, with subsequent desquamation and postinflammatory hyperpigmentation.[10]
- The multikinase inhibitors sorafenib and sunitinib cause a slightly different hand-foot reaction, named **hand-foot skin reaction (HFSR)**, with edema, hyperkeratotic lesions, and superficial blistering typically surrounded by a peripheral halo of erythema. The lesions usually affect the flexural surfaces of the digits, the pressure areas of palms and soles, and heel. The exact pathomechanism of HFSR is not known. Inhibition of platelet-derived growth factor receptor (PDGFR) and c-KIT receptors on human keratinocytes by multitargeted kinase inhibitors (MKIs) has been postulated to cause HFSR. It has been hypothesized that MKIs are excreted in the sweat glands resulting in direct skin toxicity, thus making palms and soles most vulnerable for the reaction.[11]
- **Acral pigmentary changes.** A wide variety of acral pigmentary changes may be seen as a reaction to chemotherapeutic agents. Some agents cause acral hyperpigmentation, especially bleomycin, cyclophosphamide, and doxorubicin, whereas others induce photosensitivity and darkening of sun-exposed areas. The most dramatic change is the flagellate hyperpigmentation associated with bleomycin, where dermal melanin deposition produces lesions that resemble the whiplash-like marks left after an attack by a large jellyfish. Another puzzling reaction is the cutaneous hyperpigmentation overlying veins in patients treated with 5-fluorouracil. Some patients develop many new melanocytic nevi during treatment. Others may show multiple longitudinal pigmented nail stripes, suggesting increased activity of nail fold melanocytes (especially bleomycin and methotrexate).[10]
- **Nail changes.**[10,12] See Table 1.
- **Extravasation reactions.** Many therapeutic agents are highly toxic; if they extravasate into the skin during intravenous infusions, marked damage may ensue. The worst reactions are seen with doxorubicin and daunorubicin; other culprits include vincristine, vinblastine, and actinomycin D. Pain, erythema, and swelling are the first signs; if any of these are noted during an infusion, the procedure should be stopped. A minor variant of extravasation is toxic phlebitis.[10]

Prevention and treatment of cutaneous reactions to chemotherapeutic agents

The prevention and treatment of cutaneous reactions are essential to improve the quality of life of patients with cancer and to avoid unnecessary dose modifications that may affect treatment outcome.