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Case Report

Cutaneous Toxicity in a Laboratory Beagle (*Canis lupus familiaris*) after Chronic Administration of Doxorubicin Hydrochloride

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An adult female beagle (*Canis lupus familiaris*) used in a model of doxorubicin-induced cardiomyopathy presented with epithelial desquamation on the shoulders and ventrum after receiving the 8th weekly intravenous dose of the free form of doxorubicin (20 mg/m^2; total accumulation, 160 mg/m^2). The lesions were empirically treated with topical disinfectants and topical and systemic antibiotics. Despite treatment, the lesions progressed and ulcerated. Bacterial culture revealed *Staphylococcus aureus*, but trichogram, skin scraping, and fungal culture were negative for microorganisms. Skin biopsies revealed epidermal and apocrine gland hyperplasia, apocrine gland dilation, abnormal maturation of epithelial keratinocytes, and perivascular lymphocytic infiltration. These histopathologic findings resemble those in humans and canines after chronic administration of doxorubicin-containing pegylated liposomes. Here we report a clinical presentation after chronic administration of the free form of doxorubicin. In dogs, cutaneous toxicity after administration of pegylated liposomal doxorubicin is most often localized to the footpads, limbs, and axillary and urogenital regions. In the current case, lesions affected the ventrum and trunk but did not involve the footpads or axillary or urogenital regions.

Abbreviations: doxoHCl, doxorubicin hydrochloride; PPES, palmoplantar erythrodysesthesia

Doxorubicin is a cytotoxic anthracycline antibiotic whose clinical value as an antineoplastic agent was first recognized in 1969.[26] Since that time, its ability to inhibit DNA synthesis, particularly in tissues with high turnover rate, has widely been used in the treatment of various malignant neoplasms. Dose-dependent cardiotoxicity is a well-known adverse effect of chronic doxorubicin administration and typically presents as irreversible cardiomyocyte damage that progresses to systolic dysfunction and dilated cardiomyopathy.[17] Other known adverse effects of doxorubicin include myelosuppression, gastroenteritis, and alopecia.[27,31] The development of liposomal drug-delivery systems has made it possible to refine the targeted effects of chemotherapeutic agents. In particular, compared with the free form of the drug, pegylated liposomal doxorubicin has prolonged plasma half-life and distribution into tissues, which are thought to contribute to enhanced tumoricidal effects[6,28,38] by concentrating at the tumor site and increasing the exposure of the tumor cells to doxorubicin. These altered pharmacokinetics of pegylated liposomal doxorubicin reduce the drug's cardiotoxicity in both dogs and humans[21,24,25,28,39] but enhance the development of cutaneous toxicity, compared with free doxorubicin.[27]

In humans, this cutaneous toxicity manifests as clinical syndromes including palmoplantar erythrodysesthesia (PPES), intertriginous epidermal dysmaturation, eccrine squamous syringometaplasia, and stomatitis–esophagitis,[3,7,14] with the majority of reports describing PPES. Lesions associated with PPES are typically localized to the palmar and plantar surfaces of the hands and feet[13] and are clinically characterized by erythema, desquamation, and ulceration. In dogs, chronic administration of pegylated liposomal doxorubicin can cause a similar cutaneous reaction, with lesions manifesting at sites of skin contact, including the footpads, axilla, and inguinal regions.[30] Here, we report cutaneous toxicity in a beagle after chronic administration of the free form of doxorubicin, with lesions exclusively localized to the shoulders and ventrum.

Case Report

A 3-y-old female intact beagle (*Canis lupus familiaris*) was acquired in good health from a commercial supplier of purpose-bred canines. She was singly housed at an AAALAC-accredited facility and enrolled in a research study investigating the value of noninvasive assessment of cardiac microvasculature injury for early detection of doxorubicin-induced cardiotoxicity over the course of chemotherapy treatment by using single-photon-emission-CT–CT of radiolabeled RBC.[19] All experimental procedures performed on this beagle were approved by the Yale University IACUC. In accordance with the protocol, this beagle received weekly intravascular administration of the free form of doxorubicin hydrochloride (doxoHCl; Sagent Pharmaceuticals, Schaumburg, IL) through a vascular access port, with the tip of the catheter positioned within the cavoatrial junction. The vascular access port was placed in the subcutaneous tissue between the scapulae on the dorsal midline. The port and catheter remained patent throughout the study, and no complications were observed.

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After weekly confirmation of sufficient neutrophils (>2000/µL), the beagle received doxoHCl (20 mg/m^2) for a total cumulative dose of 260 mg/m^2 over 13 wk, according to the study model, to achieve progressive systolic dysfunction. To manage potential adverse side effects associated with chronic doxoHCl administration, supportive care was initiated at the start of the study in the form of prophylactic daily enrofloxacin (5 mg/kg PO or IM; Bayer Animal Health, Shawnee Mission, KS), and ondansetron (0.8 mg/kg PO or IV; Hospira, Lake Forrest, IL) was provided as needed for mild gastrointestinal upset. After the 5th weekly administration of doxoHCl, patchy alopecia arose on all 4 limbs and the muzzle, and hyperpigmentation was most notable on the inner pinnae. In addition, the dog developed mild bilateral otitis externa. Cytology confirmed the presence of budding yeast consistent with *Malassezia pachydermatis*, which was successfully treated with a 1-wk course of an otic ointment containing gentamicin, betamethasone, and clotrimazole (Otomax, Merck Animal Health, Summit, NJ).

Three weeks later, after the 8th dose of doxoHCl, a 1×3-cm area on the left shoulder and a 4× 5-cm lesion on the ventral chest, consistent with epithelial desquamation, were observed. The lesions were cleaned with povidone–iodine solution, and daily topical neomycin–polymyxin B–bacitracin ointment was initiated. In addition, systemic antibiotic therapy was changed from enrofloxacin to cefpodoxime (5 mg/kg PO daily; Aurobindo Pharma, East Windsor, NJ). Two weeks later, the topical antibiotic ointment was discontinued and replaced by daily topical Duoxo seborrhea microemulsion spray with 0.2% phytosphingosine (Ceva Animal Health, Lenexa, KS). Despite initial treatment, by the 11th week of doxorubicin administration, the regions of epithelial desquamation on the left shoulder and ventrum had increased in size, and a similar lesion developed on the right shoulder. In addition, within this desquamation, smaller areas of erythema and ulceration of the dermis began to develop and appeared sensitive on palpation. Carprofen (0.8 mg/kg PO; Pfizer, New York City, NY) was initiated for 1 wk, and phytosphingosine-containing spray was discontinued, to limit interference with skin-sample collection and results.

After a 3-d washout to clear the phytosphingosine-containing spray, the dog was sedated by using dexmeditomidine (0.01 mg/kg IM; Orion Pharma, Finland) and maintained on 2% isoflurane in oxygen for sample collection of bacterial and fungal cultures, deep and superficial skin scrapings, trichogram, and skin biopsies. The area of desquamation on the left shoulder had enlarged to approximately 5×15 cm and contained two 0.5-cm^2 areas of ulcerated and erythematous dermis (Figures 1 and 2 A). On the right shoulder, the desquamation was approximately 4×13 cm, with a 0.3-cm^2 area of ulcerated dermis (Figure 1). Desquamation on the ventrum had extended from the midthorax to the midabdomen and measured 4 ×15 cm (Figures 1 and 2 B). Within this desquamated skin was a central 3×9 cm area of ulceration and erythema. No skin lesions were present in the axillary and inguinal regions or the footpads (Figure 2 C).

Skin biopsies were collected as follows. By using a 4-mm biopsy punch, samples were collected from the ulcerated lesions on the shoulders and ventrum and fixed in a 10% formalin solution (Figure 1). Each biopsy site was locally-blocked with 2% lidocaine and closed with a single simple interrupted suture of 3-0 polydioxanone. Buprenorphine (0.1 mg/kg SC ; PAR Pharmaceutical, Woodcliff Lake, NJ) was administered for postbiopsy pain management, and carprofen was continued as described earlier.

A pure population of *Staphylococcus aureus* grew on bacterial culture. No microorganisms were found in the fungal culture,

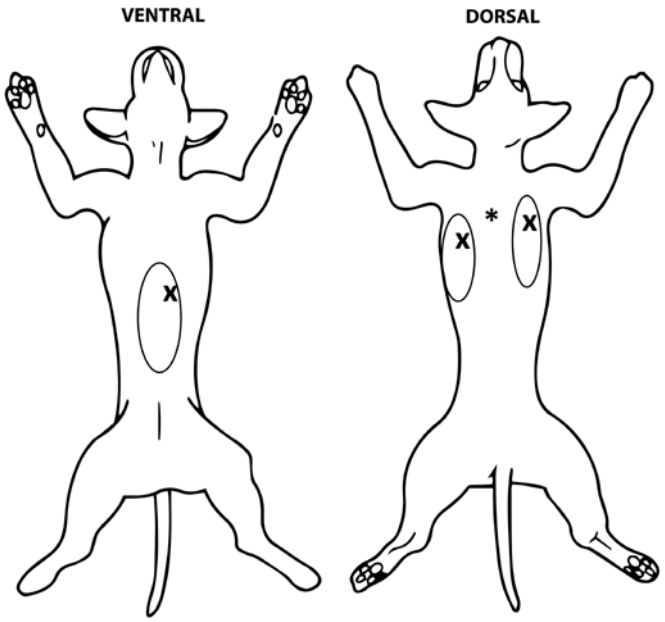

Figure 1. Overview of distribution of lesions and skin biopsy sites after the 12th weekly administration of doxorubicin HCl (total accumulation, 240 mg/m^2). *, location of the vascular access port. Lesions (ovals) were localized to the right and left shoulders and on the ventrum, from the midthorax to midabdomen. Skin biopsies (X) were taken from ulcerated lesions on each of the shoulders and ventrum.

superficial and deep skin scrape, or trichogram. Biopsy samples were embedded in paraffin, sectioned, and subsequently stained with hematoxylin and eosin as well as for markers of proliferation (Ki67) and apoptosis (activated caspase 3). Ki67 is exclusively expressed during active phases of the cell cycle (G_1 through M phases), and a recent in vitro study found that Ki67 protein expression was increased in cells treated with doxorubicin when compared with another proliferative marker, minichromosome maintenance protein 3.[4] Caspase 3 protein is a downstream target in the caspase apoptosis pathway, and doxorubicin-induced apoptosis and activation of caspase 3 has been documented.[35]

All biopsies from grossly affected sites demonstrated similar lesions (Figures 3 and 4), comprising epidermal hyperplasia and ulceration, apocrine gland hyperplasia and dilation, and superficial perivascular lymphocytic dermatitis. No intact hair follicle bulbs or sebaceous glands were present in any of the 3 samples from affected sites. Residual suprabulbar epithelial islands were associated with condensed perifollicular collagen and keratinocyte debris. Epithelial and follicular keratinocytes exhibited abnormal maturation, with nuclear pleomorphism, karyomegaly, suprabasal mitosis, apoptosis, and vacuolar degeneration. In affected regions, proliferative (Ki67) and apoptotic (activated caspase 3) markers were expressed more frequently in apocrine, follicular, and surface epithelial cells compared to normal healthy dermis.

Discussion

Several patterns of doxorubicin-associated toxicity in epithelia have been described in humans. These include PPES,[13] intertriginous epidermal dysmaturation,[3] eccrine squamous syringometaplasia,[7] and stomatitis or esophagitis.[14] Of these, the majority of reports describe PPES, a dose-dependent side effect of a broad range of chemotherapeutic agents.[13] PPES has been associated with both the free form and pegylated liposomal

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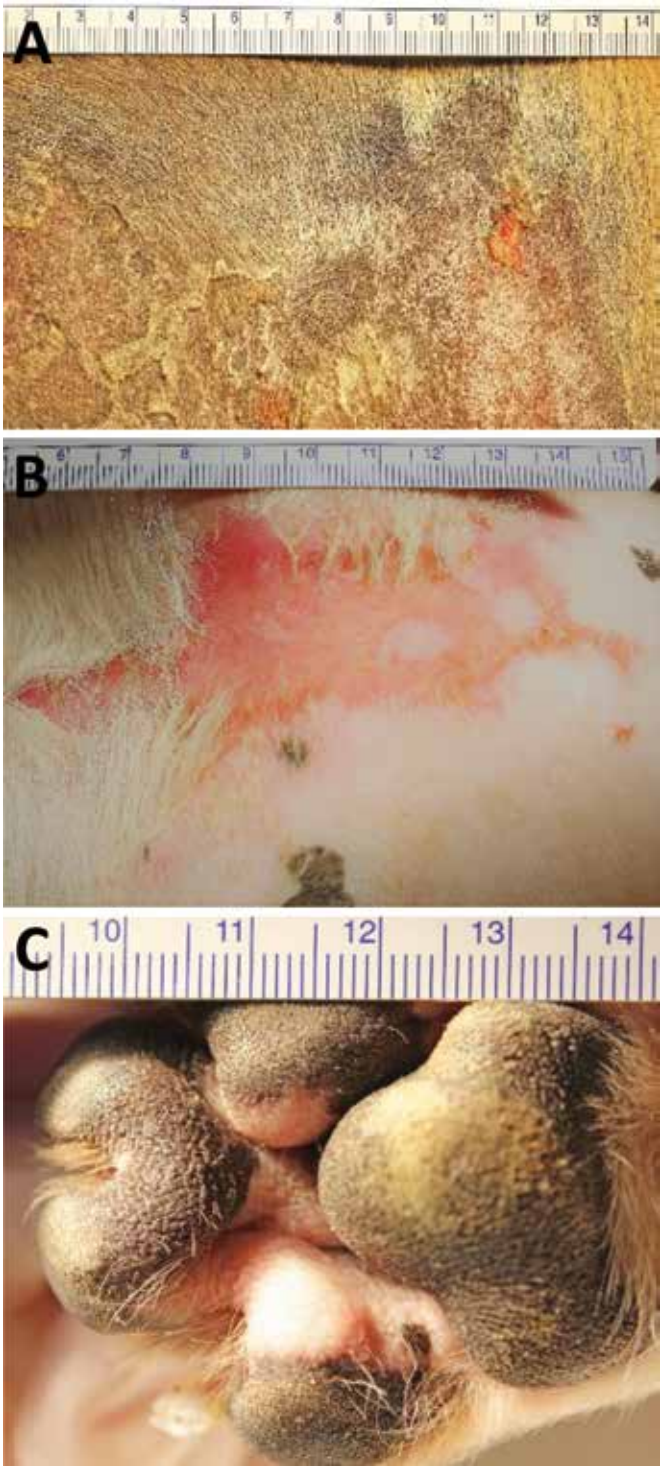

Figure 2. Cutaneous toxicity after the 12th weekly dose of doxorubicin HCl on the (A) left shoulder and (B) ventrum. Epithelial desquamation on the (A) left shoulder, with small areas of ulceration, and (B) ventrum, extending from midthorax to midabdomen, with a large area of ulceration. No lesions were observed on (C) the footpads or axillary and inguinal (not shown) regions.

formulation[12,20] but is more commonly described with the pegylated product. Similar dose-dependent cutaneous toxicity has been demonstrated with free[31] and pegylated liposomal doxorubicin in dogs.[1,27,29,30] In humans, PPES is limited to palmar and plantar erythema and edema, with various degrees of pain, scaling, and vesiculation.[13] In contrast, reports in canines describe variable erythema, scaling, and ulceration of footpads, limbs, the urogenital area and ventral body, and the head.[1,30,31] In our case, scaling erythematous lesions were located over the ventrum, shoulder, and trunk but did not involve palmar and plantar surfaces, thus resembling those noted in humans with intertriginous epidermal dysmaturation[3] and eccrine squamous syringometaplasia.[7,30]

In humans, histologic lesions of PPES are relatively nonspecific and characterized by epidermal hyperplasia, dyskeratosis, and basilar necrosis, accompanied by a perivascular or lichenoid lymphocytic superficial dermal infiltrate.[13] Although these features are evident in our dog, we noted additional histologic changes described in canine and human publications. These lesions included follicular atrophy and alopecia reported in dogs[30,31] and marked cytologic atypia in surface, follicular, and adnexal (eccrine) epithelium,[3,7] consistent with chemotherapy-induced epidermal dysmaturation.

Several pathogenetic mechanisms of anthracycline-induced cutaneous toxicity have been proposed.[16] One explanation posits that doxorubicin extravasates through endothelial cells and that highly vascularized regions with repeated low-level friction and trauma, such as hands and feet, may be predisposed to toxicity of overlying epithelium. Cutaneous toxicity, once initiated, is accompanied by dermal inflammation and vascularization that may perpetuate injury through this mechanism. Alternatively, doxorubicin and its metabolites may escape with sweat onto the skin surface,[11] where these compounds penetrate into the stratum corneum to induce surface and follicular injury.[23] In this scenario, anatomic distribution of toxicity would correlate with the distribution of different adnexal structures. In humans, eccrine sweat glands are concentrated on palmar and plantar surfaces, and demonstrated lesions within these structures[7] would support this theory. In dogs, eccrine (alternately termed atrichial) glands are located only in the foot pad, whereas apocrine (alternately termed epitrichial) glands are associated with hair follicles and diffusely distributed across the haired skin.[18] The distribution and nature of the lesions in the dog we present are consistent with sweat gland (in this case predominantly apocrine) excretion and epithelial toxicity of doxorubicin.

Since the discovery of anthracycline-induced cutaneous toxicity several decades ago, multiple treatment strategies have been investigated.[15] Studies in both dogs and humans have suggested that pyridoxine (vitamin B_6) can diminish the clinical manifestations of PPES.[29,33,34] Pyroxidine is thought to be important in a number of cellular functions, but its protective mechanisms against PPES induced by pegylated liposomal doxorubicin are unclear. Reports investigating urea-based creams, which increase hydration in the stratum corneum and improve epidermal barrier function,[9] have indicated that prophylactic treatment with these creams is efficacious in reducing the incidence and delaying the onset of PPES,[22] whereas other studies suggest that treatment is unsuccessful if initiated after clinical signs are apparent.[37]

Phytosphingosine is a natural sphingolipid component of the stratum corneum and has been suggested to facilitate homeostasis of the epidermal barrier.[36] In fact, sphinoglipids are known to play a role in a variety of functions within the epidermis, including apoptosis, cell differentiation and growth, and inhibition of inflammation.[8,10] In our case, seborrhea microemulsion spray with 0.02% phytosphingosine was initiated with the anticipation that it would facilitate epidermal repair and healing; however, epidermal lesions progressed despite this treatment. Importantly, total accumulation of doxoHCl (160 mg/m^2) at the onset of the lesions in our case was greater

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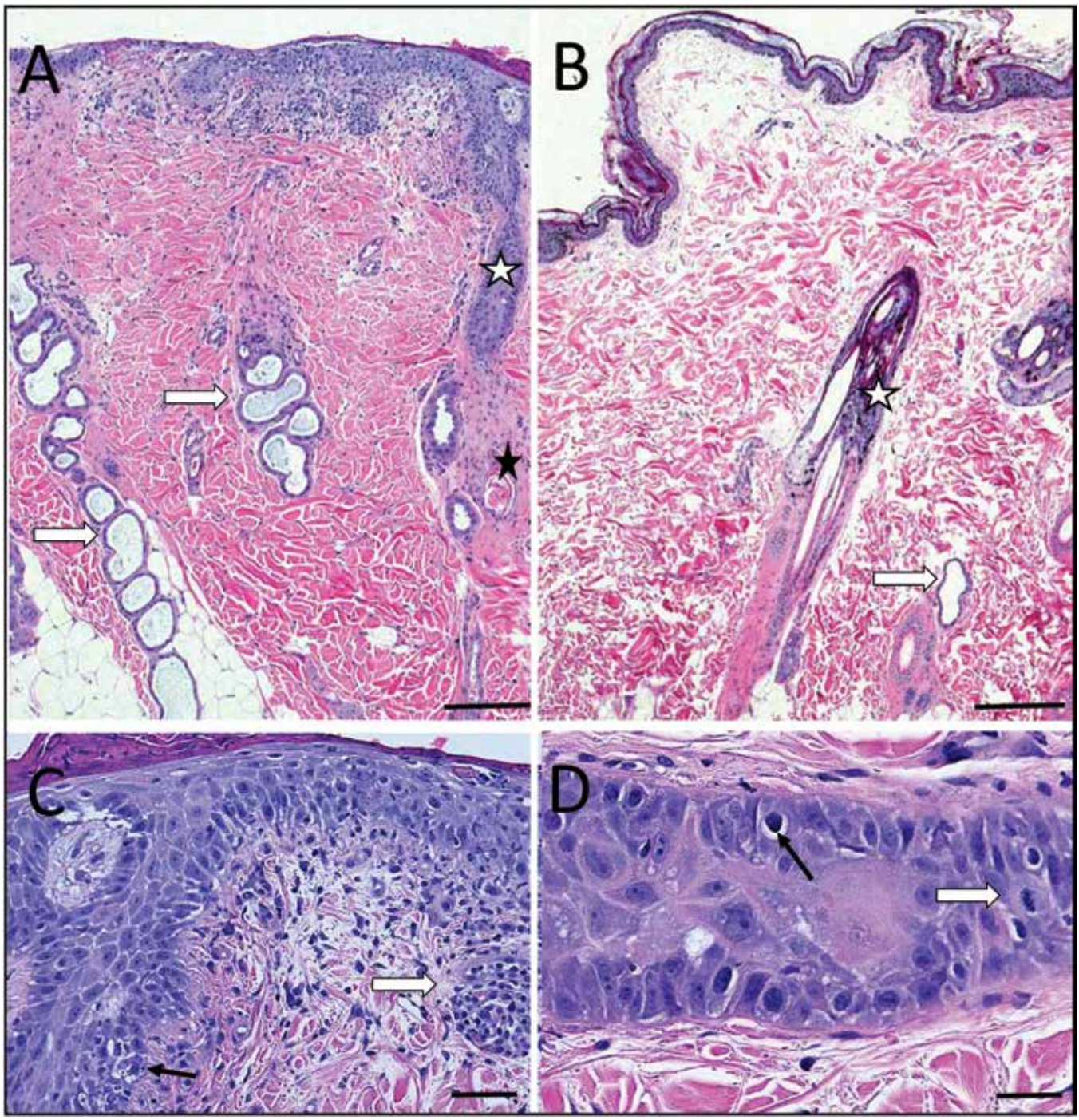

Figure 3. Overview of pathology in (A and C) affected and (B and D) unaffected regions (A) Grossly affected regions demonstrate epidermal hyperplasia, focal ulceration and superficial perivascular dermatitis. Hair follicle bulbs (black asterisk) are absent, but suprabasal regions (white asterisk) remain. (A, B) Dermatitis is accompanied by marked hypertrophy and ectasia of apocrine glands (white arrows). (C) Epithelial changes include hyperplasia, basal necrosis (black arrow) and superficial dermatitis, with perivascular round cell infiltration (white arrow). (D) Epithelial and follicular keratinocytes exhibit abnormal maturation, with nuclear pleomorphism, karyomegaly, suprabasal mitosis (white arrow) and apoptosis (black arrow) and vacuolar degeneration. Hematoxylin and eosin stain; bar: 200 µm (A, B); 50 µm (C); 25 µm (D).

than that typically achieved in a clinical setting for treatment of neoplasia in dogs,[1,30] and administration of doxoHCl continued throughout palliative treatment attempts. Although the efficacy of topical phytosphingosine-containing spray in treating doxorubicin-induced skin lesion has not been evaluated formally, we speculate that the factors just described may have contributed to failure of the spray to repair the epidermis in our case.

Dermal inflammation is a consequence of cutaneous toxicity, and NSAID have therefore been proposed as a therapeutic to provide relief from this inflammation. In fact, celecoxib, a COX2 inhibitor, has been shown to reduce the severity of clinical signs associated with mild to moderate PPES in a recent human clinical trial.[40] Because evaluation of the cellular mechanisms of cardiotoxicity was an important goal of the study in which this beagle was enrolled, long-term treatment with NSAID was avoided to prevent this confounding variable. As such, the dog received a limited 1-wk course of the NSAID carprofen for treatment of the inflammation associated with the skin lesions.

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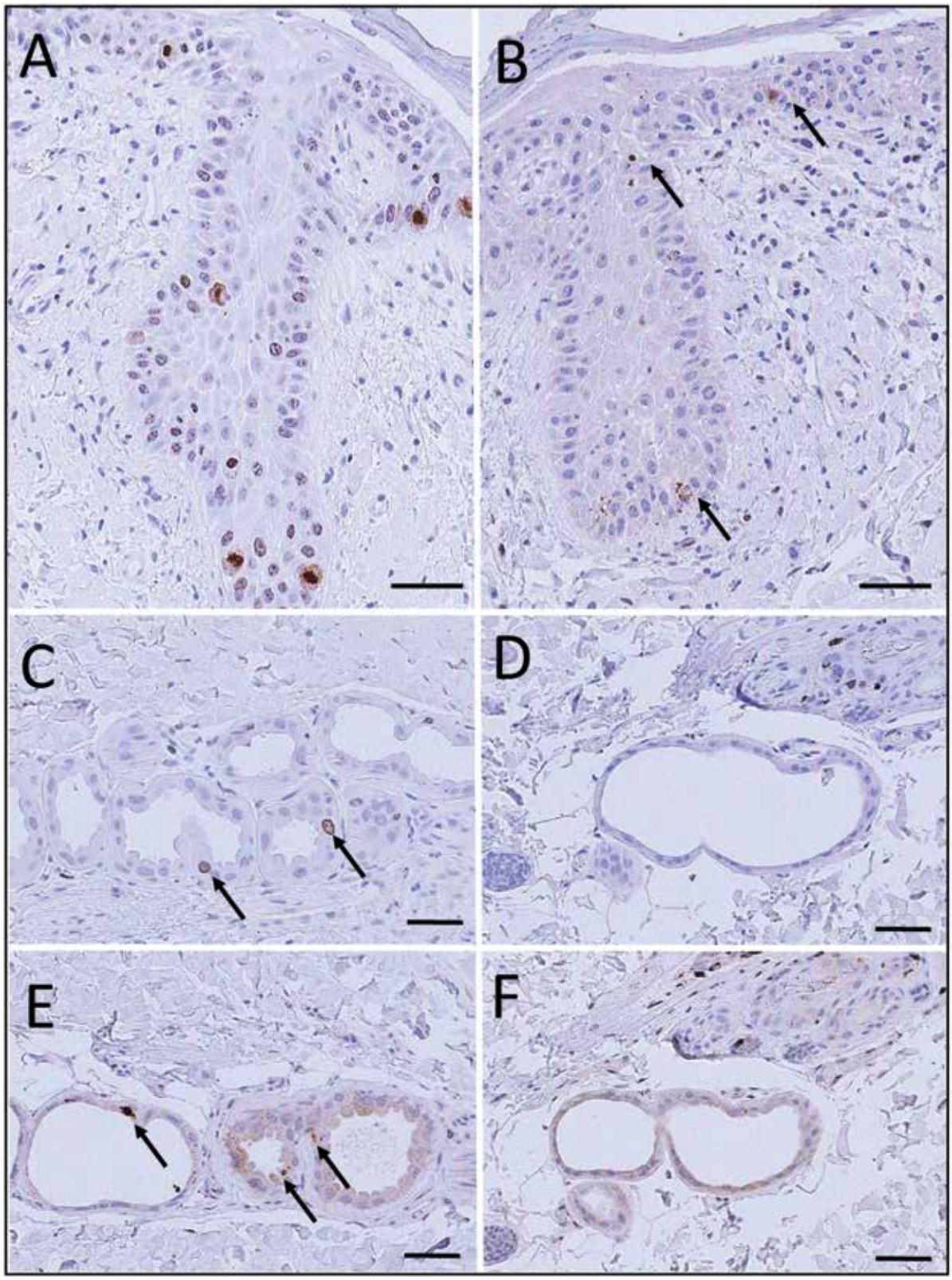

Figure 4. Apocrine gland pathology in affected and unaffected regions. Epithelial hyperplasia and dysplasia is accompanied by expression of (A) proliferative (Ki67) and (B) apoptotic (activated caspase 3) markers in basal and suprabasal layers of surface and follicular epithelium. Apocrine glands in (C, E) grossly affected regions are hypertrophic and demonstrate increased expression of (C) proliferative (Ki67) and (C) apoptotic (activated caspase 3) markers compared with those in (D, F) respectively stained unaffected regions. Bar, 50 µm.

Conclusion

Although the described treatments may facilitate a reduction in clinical signs of PPES, no therapeutic regimen to date has been shown to completely prevent or reverse anthracycline-induced dose-dependent cutaneous toxicity. In humans, severity of PPES has been categorized by the National Cancer Institute into grades 1 through 3, with grade 1 encompassing minimal skin changes, such as erythema, edema, and hyperkeratosis

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without pain, whereas grade 3 equates to severe skin changes with pain, including blisters, bleeding, swelling, hyperkeratosis, and limited ability to perform daily activities.[2] Accordingly, chemotherapeutic dose reduction and interruption has remained a mainstay for management of PPES, particularly in moderate to severe cases.[5,32] A similar grading system of cutaneous toxicity has been reported for dogs, and a dose intensity of 0.25 mg/kg weekly has been suggested to result in moderate cutaneous toxicity that is manageable with palliative care.[1] In our case, this proposed tolerable dose would have been equivalent to 5 mg/m^2 weekly, which is 25% of the weekly doxoHCl dose used for this study. Although dose reduction or interruption may have diminished the observed cutaneous toxicity in this dog, the continual doxoHCl administration was necessary to achieve the study model.

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