



# Clinical and Laboratory Findings of Induced Contact Dermatitis in Egyptian Baladi Dogs

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**Abstract:** Irritant contact dermatitis (ICD) in five healthy male Baladi dogs was induced by spraying sodium hypochlorite 5.25% for successive 16 days. Dogs were subjected to clinical examination, serum biochemical analysis of total antioxidant capacity (TAC) and C-reactive protein (CRP) as well as complete blood cell count (CBC) analysis before and after spraying and treatment. Histopathological examination of resulting skin lesions was investigated. The results revealed the appearance of erythema, alopecia, and slight congestion of the conjunctival mucus membrane. A significant decrease ( $p < 0.05$ ) in TAC was recorded at day 16 post-spraying where obvious lesions were observed. No significant change in hematological and serum CRP values was recorded. Loss of stratum corneum, hemorrhage, necrosis of the epidermal cells associated with inflammatory cell infiltration in the epidermis and the dermis, congestion of the dermal capillaries, and acanthosis were observed. The dogs were treated for 14 days using topical tacrolimus, an antihistaminic drug (Cetirizine dihydrochloride), and fatty acids (omega 3 plus). It can be concluded that routine use of sodium hypochlorite 5.25% without dilution in household cleaning solution can lead to ICD. Decreased serum levels of TAC are mainly responsible for the progress of clinical signs. Topical tacrolimus was an effective drug for contact dermatitis. The work aimed to induce irritant contact dermatitis by sodium hypochlorite 5.25% and determine any change in the hematology and sero-biochemical parameters as well as histopathological examinations. Also, how to manage and treat resulting skin lesions.

**Keywords:** Dogs; Irritant contact dermatitis; Sodium hypochlorite; TAC; Tacrolimus

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## 1. Introduction

Contact dermatitis is an inflammatory response of the skin brought on by contact with a particular substance. There are two types of contact dermatitis: irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD) (Prakash and Davis, 2010;

Rustemeyer et al., 2011; Jhones and Horn, 2014; Tan et al., 2014).

Irritant contact dermatitis is a non-specific inflammatory cutaneous reaction following direct contact with an irritating substance. Irritant contact dermatitis reactions are dose-dependent and can affect anyone. Allergic contact dermatitis is described as an immune-mediated antigen-specific inflammatory skin reaction following contact with a specific allergenic substance (sensitizer); allergic contact dermatitis reactions are idiosyncratic and not dose-dependent (Prakash and Davis, 2010).

The acute clinical signs in both irritant and allergic contact dermatitis are edema, erythema, and papules, while scaling, fissuring, and lichenification are signs of chronic lesions. Both irritant and allergic contact dermatitis may develop secondary bacterial pyoderma and/or Malassezia dermatitis as a result of self-trauma (Ho et al., 2015).

Total antioxidant capacity (TAC) is an analytical technique that is widely used to assess the antioxidant balance in biological samples (Fraga et al., 2014). Antioxidants are molecules that prevent the damaging action of oxidants, shielding cells from the oxidative damage caused by reactive oxygen species (Espinosa-Diez et al., 2015).

C-reactive protein (CRP) is an inflammatory marker, is synthesized mainly by the liver as part of the acute-phase response (Holm et al., 2004). It is mostly produced after pro-inflammatory stimulation by cytokines such as IL-1, IL-6, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) (Paul et al., 2011).

## 2. Materials and Methods

### 2.1. Animals and experimental design

Five healthy male Baladi dogs were randomly selected, 3-4 years old and 13-20 kg Bwt. and fed on bread and legs of chicken. They were kept in the Clinic of the Internal Medicine Department, Faculty of Veterinary Medicine, Damanhour University. The ethical committee of the Faculty of Veterinary Medicine, Damanhour University (DMU-VET MED-2023-041) approved the research protocol.

The study lasted for 30 days. All dogs were subjected to spraying the skin with sodium hypochlorite 5.25% (Clorox<sup>®</sup> - The Egyptian Company for Household Detergents) for successive 16 days. These dogs underwent clinical examination and blood sampling at zero-day (group I) before spraying and day 2 (group II), day 16 (group III) post spraying, and at the end of the experiment (group IV) after receiving the treatment which started after last spray and continued to the end of the study.

### 2.2. Hematological and sero-biochemical analysis

Two blood samples were collected from the cephalic vein of each dog. The first one was collected in an evacuated vacutainer containing anti-coagulant ethylene diamine-tetra-acetic acid (EDTA) for complete blood cell count analysis (CBC) by using Auto analyzer/Cell counter Mindray BC-2800vet, France (Jain, 2000). The second one was collected (without EDTA) for sero-biochemical determination of TAC and CRP. TAC was measured using an automated colorimetric measurement method (Erel, 2004), while CRP was measured by immunoturbidimetric assay (Katarzyna and Olga, 2022). UV spectrophotometer used for measurement of both TAC and CRP.

### 2.3. Skin examination

Skin specimens were collected for histopathological examination at day 16 (group III) where the severity of clinical signs was observed. Xylazine hydrochloride in a dose of 2.3 mg/kg. was used as a muscle relaxant for collection of skin samples. Skin biopsy specimens were collected using a 4 mm circular punch at a depth of 2 mm and fixed in 10% neutral buffer formalin, washed, dehydrated, cleared, and embedded in paraffin. The paraffin-embedded blocks were sectioned at 4–5-micron thickness and stained with Haematoxylin and Eosin (H and E) for light microscopic examination (Bancroft and Gamble, 2008).

### 2.4. Treatment

The treatment was started by removing the irritant substance; washing the dogs and floor of the clinic with water then swabbing the skin lesions with normal saline 0.9% (ultimate pharma Co.), tacrolimus 0.3 mg (trezimus 0.1 ointment of mercyril pharmaceutical industries<sup>®</sup>, it is a calcineurin inhibitor that was used once daily topically. Also, Cetirizine dihydrochloride was given as an antihistaminic (Ho et al., 2015), with a dose of 0.5 mg/kg Bwt. daily. Fatty acid (1000 mg gelatine capsules omega 3 plus- sedico pharmaceutical Co.<sup>®</sup> is a dietary food supplement that is used once daily. All treatments were continued for 14 days.

### 2.5. Statistical analysis

Statistical analysis of data was fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using numbers and percentages. The Kolmogorov-Smirnov Shapiro-Wilk test was used to verify the normality of distribution. Quantitative data were described using range

(minimum and maximum), mean and standard deviation. The significance of the obtained results was judged at the 5% level (Kirkpatrick and Feeney, 2013). The used tests were the F-test (ANOVA) for normally distributed quantitative variables, to compare between more than two groups, for physical examinations (respiratory rate, heart rate, and body temperature), CBC and CRP, and Post Hoc test (Tukey) for pairwise comparisons for TAC.

### 3. Results

Erythema and loss of hair (alopecia) at the inner forearm and wrist were the most observed skin lesions in dogs at 2<sup>nd</sup> day of spraying sodium hypochlorite 5.25% (group II) (Figure 1a, b). The lesions become severe at day 16 post spraying (group III) and dermatitis is distributed in different areas; daw claws, inner forearm, upper thigh, and paw pads (Figure 2a-e). Response to treatment was observed at the end of the experiment where the skin lesions were healed in the affected dogs (Figure 3a-c).

Non-significant changes in body temperature, heart, and respiratory rates in all dog groups compared to control one were recorded (Table 1). Lymph nodes were normal; firm, smooth, and bean-shaped. The conjunctival mucus membrane was slightly congested in only three dogs in group 3 (at day 16 post spray). There was a non-significant change in hematological parameters in all dog groups compared to the control one (Table 2).

Regarding serum biochemical analysis, a significant decrease in the mean level of TAC in group III at day 16 ( $0.13 \pm 0.01$  mmol/l) compared to group II at day 2 from spraying ( $0.21 \pm 0.03$  mmol/l) and control group ( $0.24 \pm 0.02$  mmol/l) was recorded. A significant increase in the mean level of TAC in group IV after treatment ( $0.21 \pm 0.03$  mmol/l) compared to group III was observed (Table 1). Serum C-reactive protein (CRP) showed no significant changes in all groups of animals compared to the control group (Table 1).

Histopathological examinations of skin lesion showed moderate dermatitis, the epidermal cell layer showing loss of stratum conium (Keratinized cell layer), hemorrhage, and necrosis of the epidermal cells associated with inflammatory cell infiltrations in the epidermis and the dermis. One dog showed thinning of the stratum corneum (Keratinized cell layer), congestion of the dermal capillaries, and skin of a dog showing acanthosis (Thickening of the stratum spinosum) (Figures 4 and 5).

**Table 1.** Body temperature, heart, and respiratory rates in dogs before, after spraying of skin irritant and after treatment

Parameters	Group I (n = 5)	Group II (n = 5)	Group III (n = 5)	Group IV (n = 5)	F	p
Body temperature °C.	38.0 -39.0	38.0 – 38.5	38.0 – 39.0	38.0 – 39.0	2.561	0.091
	38.5 ± 0.35	38.34 ± 0.23	38.58 ± 0.45	38.94± 0.35		
Heart rates/min.	65.0 – 70.0	60.0 – 80.0	60.0 – 75.0	60.0 – 70.0	0.748	0.539
	68.0 ± 2.74	69.40 ± 9.32	65.40 ± 5.77	65.40 ± 5.78		
Respiratory rates/min.	35.0 – 48.0	35.0 – 40.0	35.0 – 42.0	38.0 –42.0	0.185	0.905
	38.60 ± 5.68	38.0 ± 2.74	39.0 ± 2.65	39.60 ±1.52		

F: F for One way ANOVA test      p: p - value for comparing between the studied groups      SD: Standard deviation.

**Table 2.** Haematological parameters in dogs before, after spraying of skin irritant and after treatment

Parameters	Group I (n = 5)	Group II (n = 5)	Group III (n = 5)	Group IV (n = 5)	P
RBCs x10 <sup>6</sup> /ul	4.84-6.15	4.52-5.88	4.22-5.4	4.64-5.86	0.348
	5.4±0.6	5.17±0.60	4.75±0.49	5.08±0.49	
Hemoglobin g/dl	11.4-13.2	11.1-12.9	10.5-11.8	11.0-12.1	0.152
	12.2±0.76	11.84±0.74	11.22±0.54	11.74±0.44	
HCT %	35.4-45.2	32.5-41.6	31.0-41.0	34.1-41.9	0.254
	39.32±4.04	36.64±3.43	34.54±4.06	37.44±2.81	
Platelets x10 <sup>3</sup> /ul	180.0-197.0	180.0-196.0	179.0-195.0	180.0-196.0	0.998
	187.4±6.88	187.2±6.53	186.6±6.50	187.0±6.40	
WBCs x10 <sup>3</sup> /ul	7.7-11.2	8.3-11.8	8.9-12.4	7.90-11.5	0.619
	9.34±1.36	9.84±1.38	10.46±1.35	9.62±1.37	
Neutrophils x10 <sup>3</sup> /ul	4.8-6.9	4.9-7.2	5.5-7.5	4.9-7.0	0.642
	5.66±0.94	5.9±1.01	6.36±0.85	5.72±0.94	

Parameters	Group I (n = 5)	Group II (n = 5)	Group III (n = 5)	Group IV (n = 5)	P
Lymphocytes x10 <sup>3</sup> /ul	2.1-3.3	2.3-3.5	2.4-3.8	2.2-3.4	0.752
	2.48±0.48	2.62±0.51	2.82±0.57	2.56±0.48	
Eosinophils x10 <sup>3</sup> /ul	0.54-0.89	0.59-0.93	0.61-0.97	0.52-0.86	0.698
	0.68±0.14	0.73±0.13	0.76±0.14	0.67±0.14	
Monocytes x10 <sup>3</sup> /ul	0.48-0.94	0.46-0.91	0.46-0.91	0.44-0.92	0.998
	0.63±0.18	0.61±0.17	0.61±0.18	0.62±0.18	

p: p - value for comparing between the studied groups.  
SD: Standard deviation.

**Table 3.** TAC in dogs before and after spraying of skin irritant and after treatment

	Group I (n = 5)	Group II (n = 5)	Group III (n = 5)	Group IV (n = 5)	P
TAC value	0.22 -0.27	0.18 -0.25	0.12 -0.14	0.18 -0.25	<0.001*
mmol/l	0.24 ±0.02	0.21 ±0.03	0.13 <sup>ab</sup> ±0.01	0.21 <sup>c</sup> ±0.03	
p1		0.143	<0.001*	0.332	
p2			0.001*	0.948	
p3				<0.001*	

Pairwise comparison bet. each 2 groups were done using Post Hoc Test (Tukey)

p: p - value for comparing between the studied groups.  
p<sub>1</sub>: p - value for comparing between Group I and each other group.  
p<sub>2</sub>: p - value for comparing between Group II and each other group.  
p<sub>3</sub>: p - value for comparing between Group III and IV.

\*: Statistically significant at p ≤ 0.05

a: Significant with Group I                      b: Significant with Group II  
c: Significant with Group III                      SD: Standard deviation

**Table 4.** CRP in dogs before, after spraying of skin irritant and after treatment

	Group I (n = 5)	Group II (n = 5)	Group III (n = 5)	Group IV (n = 5)	F	P
CRP	6.0 - 10.50	6.0 - 13.0	6.0 - 11.0	6.0 - 10.50	0.357	0.785
mg/L	8.28 ± 1.94	9.60 ± 2.70	9.20 ± 2.08	8.70 ± 1.79		

F: F for One way ANOVA test      p: p - value for comparing between the studied groups. SD: Standard deviation.



**Figure 1.** Contact dermatitis after 2 days from spray that show erythema and loss of hair, at **a**: inner forearm, **b**: wrist.

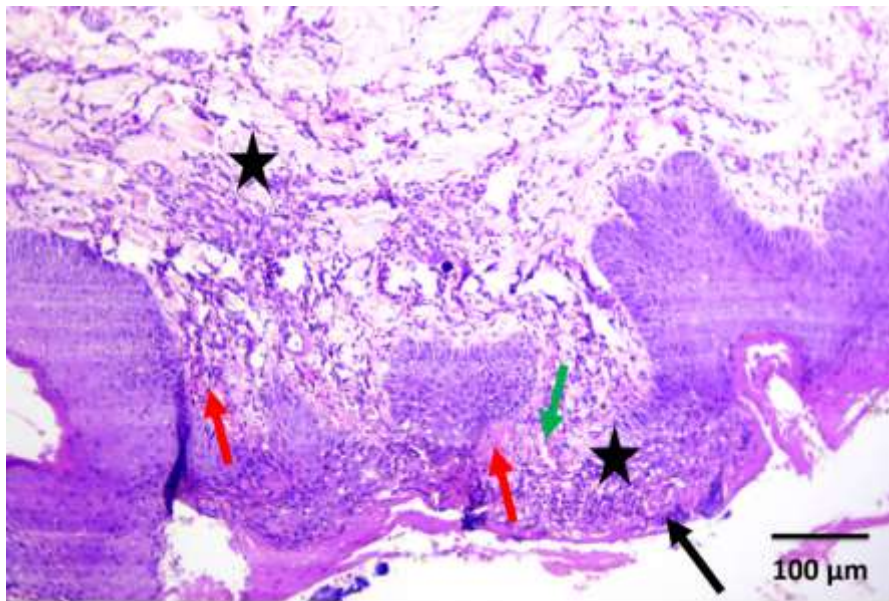


**Figure 2.** Contact dermatitis at day 16 from spray, erythema, and alopecia at **a**. paw pads, **b**. forearm. **c**. upper thigh of hind limb, **d**. upper thigh of hind limb, and **e**. paw pads.

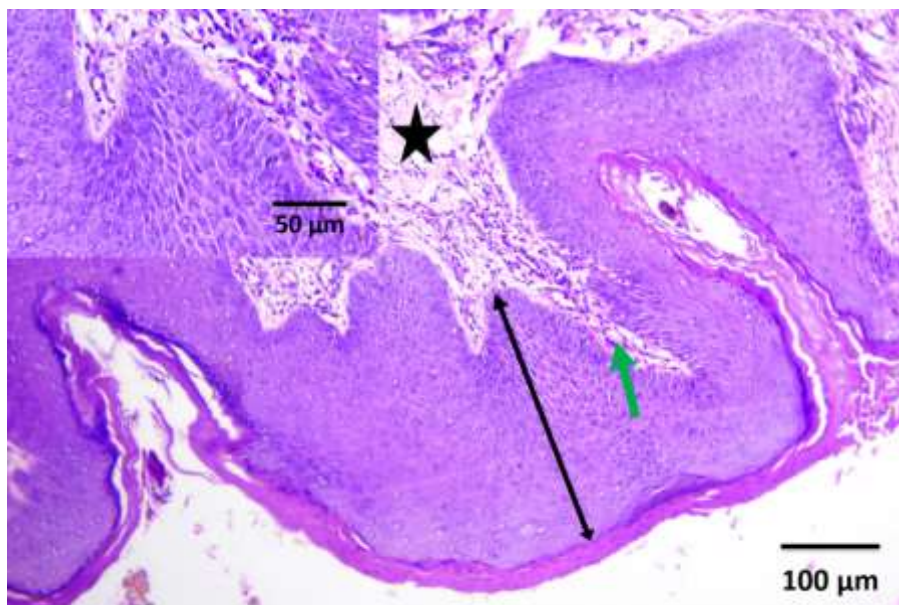




**Figure 3a-c.** Showing improvement of skin lesions after treatment in group IV



**Figure 4.** The skin of a dog shows moderate dermatitis, the epidermal cell layer showing thinning of stratum corneum (Keratinized cell layer), congestion of the dermal capillaries (green arrow), hemorrhage in the epidermal and dermal skin layers (red arrows) and necrosis of the epidermal cells (black arrow) associated with inflammatory cells infiltrations in the epidermis and the dermis (stars).



**Figure 5.** Skin of a dog showing acanthosis (Thickening of the stratum spinosum) double head arrow, congestion of the dermal capillaries (green arrow), and inflammatory cell infiltrations in the dermis (star).

#### 4. Discussion

Irritant contact dermatitis (ICD) is an inflammatory skin reaction brought on by outside factors. With various pathophysiological circumstances, natural histories, and clinical symptoms, it is regarded as a complicated biological syndrome (Bains et al., 2019). In addition, the same author reported that since it is unclear whether endogenous or exogenous factors contribute more to the development of ICD, the type of irritant, the quantity of exposure, concentration, duration, repetition, and the existence of overlapping environmental and mechanical components should all be considered while evaluating ICD.

In this study spraying of sodium hypochlorite 5.25% resulted in dermatitis with erythema and alopecia (ICD) that agreed with Bains et al (2019) who reported Soap, detergent, industrial cleaning chemicals, glue, paint, juice, plant juice, oxidizing and reducing agents, insecticides, pesticides, cement, limestone, wood preservative, formalin, bleach, acid, and alkali are some of the main substances which cause ICD. Dermal exposure to household bleach has only minor, temporary effects. Extensive or prolonged exposure may result in skin damage, skin irritation, or dermal hypersensitivity (Slaughter et al., 2019).

Sodium hypochlorite (household bleach) is an alkaline solution that has a pH between 11 and 12. It is commonly sold at a 5.25% concentration, with more concentrated forms suitable for heavy-duty and pool cleaning purposes (Kawalilak et al., 2017).

Bleach solutions containing sodium hypochlorite are mostly used and generally considered to be safe cleaning products. In contrast, The U.S. Department of Health, Agency for Toxic Substances and Disease Registry (2006) mentioned that hypochlorite moiety has a toxic effect causing deep tissue damage through saponification of proteins and fats and liquefactive necrosis (Caroline et al., 2007).

Sodium hypochlorite causes lesions by two mechanisms: alkalinity and oxidoreduction (Telmon et al., 2002). Alkali substances react with cell membrane lipids and destroy glycosaminoglycan ground substance via saponification, disrupting cells, and causing softening of the tissue and keratocyte devitalization. Liquefactive necrosis is the result, which loosens tissue planes and allows the alkali agent to infiltrate deeper. A tissue pH elevation of 5.9 units above normal results from the alkaline solution's pH aberration, which lasts about 12 hours (Gruber et al., 1975). Alkalis also dry the skin due to a hygroscopic characteristic that causes cellular death and dehydration (Bromberg et al., 1965). Within a few hours, oxidoreduction-related lesions are caused by cutaneous protein coagulation (Piggott et al., 2007). This explains the causes of the demonstrated skin lesions in the present study.

Group II showed erythema and loss of hair at the inner forearm and the wrist, which became more severe and more distributed on day 16 post-spraying (Group III), these results are similar to Ho et al (2015), who reported that lesions that develop from ICD typically develop only in the area of direct contact and are well demarcated, acute lesions include oedema, erythema and papules.

ICD lesions will more commonly cause ulceration and epidermal necrosis. Lampel and Powell (2019) reported that Wide-ranging morphological alterations associated with ICD are most prominently seen in the skin, where erythema, edema, desquamation, and keratinocyte vesiculation occur in the acute phase Skin lesions appeared at specific sites such as hock, inner forearm, upper thigh, inner upper thigh, daw claws and paw pads. These results were in agreement with Ho et al (2015). No significant change in both body temperature and heart and respiratory rates in all dogs' groups compared to the control group (day zero) was recorded and this agreed with Debra et al (2007). Palpable lymph nodes in dogs of all groups were normal, typically firm, smooth, and bean-shaped in agreement with Tanya and Michelle (2016).

The appearance of slightly congested conjunctival mucus membrane on the 16<sup>th</sup> day after the spray was agreed with Celentano et al (2016), who reported that household bleach generally doesn't cause marked ocular effects following eye

exposure, only mild to moderate corneal injuries, accompanied by burning sensation and a superficial disruption of the corneal epithelium which healed within one or two days.

Our result revealed a significant decrease in the mean level of TAC at day 16 post-spraying, this result agreed with Baek and Min-Geol (2016), who reported that serum total antioxidant status values were significantly reduced in seborrheic dermatitis patients. Reactive oxygen species play an important role in the appearance of both forms of contact dermatitis (Kim et al., 2012). ROS initially mediate modifications to the extracellular matrix that aid allergic contact dermatitis (ACD) (Agren et al., 1997). ROS are produced by keratinocytes and almost all kinds of skin cells in response to signals from cytokines, growth factors, airborne pollutants, UV radiation, food additives/preservatives, cosmetics, drugs, and physiologic stimuli (Pai et al., 2014). ROS include superoxide anion ( $O_2^{\ominus}$ ), peroxides, hydroxyl radical ( $OH^{\circ}$ ), and singlet oxygen ( $^1O_2$ ) (Chen et al., 2012). These molecules in certain quantities activate proliferative and cell survival signaling although their high levels cause damage to DNA, lipid membranes, collagen structures, and mitochondrial function (Baek and Lee, 2016). Antioxidants are classified as endogenous and exogenous. The skin has a vast antioxidant system, including enzymatic antioxidants and non-enzymatic antioxidants (Pai et al., 2014). The synthesis of antioxidant enzymes also rises when ROS levels are excessively high to safeguard the organism's structural and functional integrity (Pastore and Korkina, 2010) and decrease the harmful effects of ROS in the body (Karaca and Guder, 2009). Reduced levels of antioxidants may signal an overproduction of oxidants that damage DNA, lipids, and proteins, a condition known as oxidative stress (Espinosa-Diez et al., 2015).

At the end of the experiment after treatment and healing of the skin significantly increased compared to group III and became closer to that of group one (control group). This may explain as during the period of the treatment antioxidant enzymes were induced, inflammation of irritant contact dermatitis decreased, and oxidative stress reduced.

Serum CRP showed non-significant changes in all groups of animals compared to the control group which agreed with Loo et al (2003) who reported that CRP was normal in patients who had irritant dermatitis with another chemical substance such as oilatum plus. Moller et al (1999) also reported that C-reactive protein did not increase in any of the patients with contact allergy to nickel or gold. The non-significant change in serum CRP may be due to delayed time for its analysis at 2 days post spray as CRP blood concentration varies significantly within 4-6 hours after the inflammatory stimulus and reaches its peak concentration after around 24-48 hours (Katarzyna and Olga, 2022).

Regarding hematological analysis, there were non-significant changes in CBC in diseased groups compared with the control group and after-treatment group. These results were in agreement with that reported by Kawalilak et al (2017) in neutered male Fox Terrier 5 days after sticking his muzzle into a toilet bowl that had recently been cleansed with sodium hypochlorite 8.25%. Moreover, our results agreed with Alena (2009), who used cement, and Loo et al (2003), who used oilatum plus as they reported that the hematological findings were normal in patients who had irritant contact dermatitis. Karadag et al (2011), reported that irritant contact dermatitis with leeches had normal hematological results.

So, we can conclude that CBC analysis is not an indicator for diagnosis of irritant contact dermatitis as Brans et al (2021), recorded that there was no common test or biomarker for ICD.

Histopathological examination of the skin lesion showed moderate dermatitis, the epidermal cell layer showing loss of stratum corneum (Keratinized cell layer), hemorrhage, and necrosis of the epidermal cells associated with inflammatory cell infiltrations in the epidermis and the dermis. Another one showed the epidermal cell layer showing thinning of the stratum corneum, congestion of the dermal capillaries, and Thickening of the stratum spinosum (acanthosis), This agreed with Gross et



al (2005), who reported that histopathology of irritant contact dermatitis shows some degree of epidermal degeneration due to its direct cellular damage to keratinocytes.

Weedon et al (2010) reported that variable degrees of superficial perivascular dermatitis, neutrophilic epidermal spongiosis, and epidermal ulceration and necrosis may be present in acute lesions. There may also be lymphocytes and macrophages in the cellular infiltration.

Tacrolimus topical ointment was used for the treatment of irritant contact dermatitis as Mark and Warren (2018) reported that the first-line treatments of ICD consist of physical protection of skin, protective cream/emollient, topical tacrolimus/pimecrolimus. According to a double-blinded controlled examination, 95% (18 patients) of those with allergic contact dermatitis to nickel improved clinically after receiving topical tacrolimus 0.1% (Saripalli et al., 2003).

In another study, Tacrolimus was effective in the management of skin irritancy caused by sodium lauryl sulfate (Jungersted et al., 2011) that it is an anionic surfactant commonly used as an emulsifying cleaning agent in household cleaning products that have an irritant effect on the skin with direct contact of it (Bondi et al., 2015).

Tacrolimus a calcineurin inhibitor, inhibits the production of pro-inflammatory cytokines by interacting with the intracellular protein FKBP which has an immunosuppressive effect on mast cells and leucocytes (Arora et al., 2020). Topical tacrolimus reduces cytokine mRNA levels of IL-1 $\alpha$ , IL-1 $\beta$ , and macrophage inflammatory protein, which results in lymph node cell proliferation. Tacrolimus prevents the production and release of several cytokines, including interferon- $\gamma$ , tumor necrosis factor- $\alpha$ , granulocyte-monocyte colony-stimulating factor, IL-2, IL-3, IL-4, and IL-5. Tacrolimus also reduces the production of T-helper 1 (Th1) and Th2 cytokines (Gupta et al., 2002).

Cetirizine dihydrochloride is an antihistaminic drug for the treatment of ICD. Antihistamines were used to reduce pruritus in contact dermatitis patients, as well as to perhaps reduce inflammation and enhance barrier function, presumably because keratinocytes express histamine type 1 and type 2 receptors (Ho et al. 2015).

In our study, we used Fatty acids in the treatment. Fatty acids are important in hydration and controlling the barrier function of the epidermis. They are also keratolytic and fungistatic (Miller et al., 2013).

It can be concluded that routine use of sodium hypochlorite 5.25% without dilution in household cleaning solution can lead to ICD. TAC is a prognostic aid for cases of ICD in dogs. ICD is associated with oxidative stress which is indicated by low TAC, and it is responsible for the progress of skin lesions. An accurate clinical history is important in the diagnosis of contact dermatitis and early identification and avoidance of the irritating agent are important in the management of patients with contact dermatitis. Topical tacrolimus was an effective drug for contact dermatitis.

Further studies may be needed to determine the prevalence of contact dermatitis among dog breeds, investigate their genetic predisposition, and the role of other biomarkers in the pathogenesis of the disease.

**Conflict of interest:** There are no conflicts of interest stated by the authors.

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