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Drug eruption in a cat following the use of multiple medications to treat systemic conditions

Farmacodermia em gato após uso de múltiplas medicações para tratamento de afecções sistêmicas

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ABSTRACT: Drug eruption, also known as cutaneous adverse drug reaction, is a rare disease that is difficult to diagnose, requiring a combination of history evaluation, physical assessment, and histopathological examination. Clinically, it presents with variable signs, from mild urticaria to epidermal necrosis. Treatment consists of discontinuing the causative or similar medication; lesion management; and, sometimes, implementing systemic immunosuppressive treatments. The prognosis is generally good, except when there is systemic involvement or extensive skin necrosis. This study aims to describe the lesions, diagnosis, and evolution of a young cat presenting with drug eruption following the use of multiple medications for the treatment of systemic conditions. The patient underwent skin biopsy after showing progression of alopecic and localized lesions, which resulted in a suggestive diagnosis of superficial pustular drug eruption. Previous drug treatments were interrupted, but due to the lack of improvement in the lesion pattern, we chose to re-administer chlorambucil at a dose of 2 mg/cat every 48 h for therapeutic purposes. Up to the present time, the patient has been undergoing treatment and lesion management, with healthy-looking scar tissue and almost complete resolution of the skin lesions.

KEYWORDS: Adverse reaction; dermatitis; hypersensitivity.

RESUMO: A farmacodermia ou reação medicamentosa adversa cutânea é uma doença rara e de difícil diagnóstico, que demanda associação de histórico, avaliação física e exame histopatológico. Clinicamente apresenta sinais variáveis, desde leve urticária até necrose epidérmica. O tratamento consiste em descontinuar o medicamento causador ou semelhantes, realizar manejo das feridas e, por vezes, instituir tratamentos sistêmicos imunossupressores. O prognóstico geralmente é bom, exceto quando houver envolvimento sistêmico ou extensa lesão cutânea necrótica. O objetivo deste trabalho é descrever as lesões, diagnóstico e evolução de um gato jovem apresentando farmacodermia após o uso de múltiplas medicações para tratamento de afecções sistêmicas. O paciente foi submetido a biópsia cutânea após apresentar progressão de lesões alopécicas e localizadas, que resultou no diagnóstico sugestivo de farmacodermia pustular superficial. Foram interrompidos os tratamentos medicamentosos prévios, porém não havendo melhora do padrão lesional, optou-se pela readministração de clorambucil na dose de 2 mg/gato a cada 48 horas com objetivo terapêutico. Até o presente momento, o paciente encontra-se sob tratamento e manejo de feridas, com tecido cicatricial de aspecto saudável e quase total resolução de lesões cutâneas.

PALAVRAS-CHAVE: reação adversa, dermatite, hipersensibilidade

INTRODUCTION

Drug eruption is an uncommon cutaneous adverse reaction that is caused by the use of a drug or the interaction of two or more medications (MILLER; GRIFFIN; CAMPBELL, 2013). It can occur after the use of any medication or immunogen administered orally, parenterally, by inhalation, or topically (LARSSON; LUCAS, 2020). Manifestations of drug eruption can be observed after recent treatments or after years of use of triggering medications (HNILICA, 2011).

Clinical changes observed in affected animals are mediated by cytotoxic lymphocytes against keratinocytes altered by the drug reaction (YAGER, 2014). Clinical signs are variable and include urticaria, angioedema, erythema, desquamation, maculopapular lesions, nodules, injection site reaction, skin atrophy,

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self-induced pruritic lesions, contact reactions, and epidermal necrosis (LARSSON; LUCAS, 2020; VOGELNEST, 2017).

The diagnosis is based on the history of administration of substances potentially inducing drug eruption and the exclusion of other systemic diseases that may have cutaneous manifestations, in addition to biopsy of the injured skin fragment and histopathological examination (HNILICA, 2011).

Treatment consists of discontinuing the triggering drug, avoiding chemically similar drugs, lesion management, and implementing systemic treatments according to the severity of the lesion, using glucocorticoids or immunosuppressive drugs such as chlorambucil. The prognosis is generally good, except when other systems or organs are involved, or in the case of animals with extensive epidermal necrosis (MILLER; GRIFFIN; CAMPBELL, 2013).

The aim of this report is to describe the lesions, diagnosis, and evolution of a young cat presenting with drug eruption following the use of multiple medications to treat systemic conditions.

CASE REPORT

A one-year-and-five-month-old, 3.6-kg, male, unneutered, FIV- and FeLV-negative (Allere® rapid test) domestic cat (Felis catus) was brought to our care with a history of skin lesion for one week following the use of multiple medications for the treatment of neutrophilic cholangiohepatitis and inflammatory bowel disease.

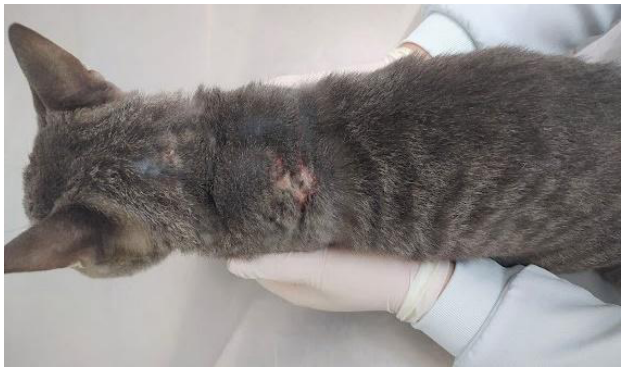
During anamnesis, the owner reported administration of amoxicillin with potassium clavulanate (20 mg/kg BID, PO), prednisolone (1.4 mg/kg BID, PO), and ursodeoxycholic acid (10 mg/kg SID, PO) for 60 days, in addition to metronidazole (15 mg/kg BID, PO), silymarin (20 mg/kg SID, PO), and S-adenosyl-L-methionine (20 mg/kg SID) for 30 days. Clinical improvement occurred only after the association of chlorambucil (2 mg/cat, PO) every 48 h, for five weeks. Previous use of multiple deworming and anti-flea agents was also reported, the most recent of which had been performed over six months before the first consultation. There was no history of vaccinations.

On physical examination, the patient exhibited mild jaundice on the palate due to cholangiohepatitis at the end of treatment, in addition to the presence of a lesion located on the left thoracic limb. Initially, it consisted of an isolated, alopecic, non-erythematous, non-ulcerated lesion of approximately one centimeter in diameter, located in the left scapular region. After one week, lesion foci in the scapular and dorsal cervical regions began to increase in diameter. The lesions remained alopecic, but ulcerated and exudative, with erythematous borders, associated with mild pruritus and absence of purulent secretion, according to the owner.

Based on anamnesis and physical examination findings, the main suspicion was drug eruption. Drug administration was therefore immediately interrupted, with gradual withdrawal of prednisolone. For diagnostic confirmation, skin biopsy of the ulcerated lesions was performed and a fragment of one centimeter in diameter was removed from the left scapular region, which had evolved for approximately one month; and from the lesion in the dorsal cervical region, which had evolved for one week (Figures 1 and 2). Prior to the biopsy, the patient had not received any medication for four weeks due to improvement in the initial clinical picture of cholangitis and inflammatory bowel disease, and had had skin lesions for six weeks.

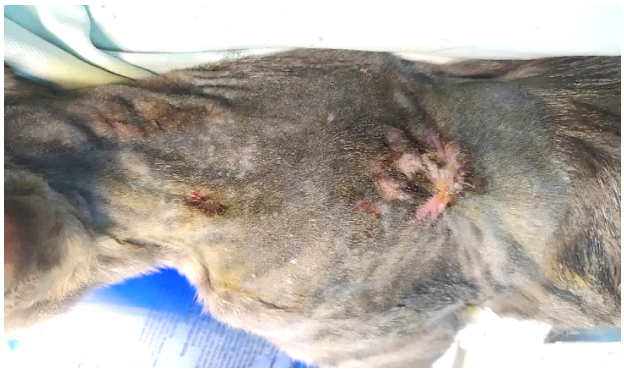
Histopathological examination of the lesions in the cervical and left scapular regions revealed a marked presence of diffuse epidermal necrosis with multifocal epidermal microabscesses and moderate spongiosis, as well as moderate diffuse pyogranulomatous dermatitis. Additionally, the histological section of the cervical lesion showed coccoid bacterial colonies interspersed with the necrotic material (Figures 3 and 4). The changes observed in the skin fragments were suggestive of superficial pustular drug eruption.

The patient remained without administration of medication for 40 days, yet with no resolution of the lesions. After this period, chlorambucil (2 mg/cat every 48 h, PO) was instituted



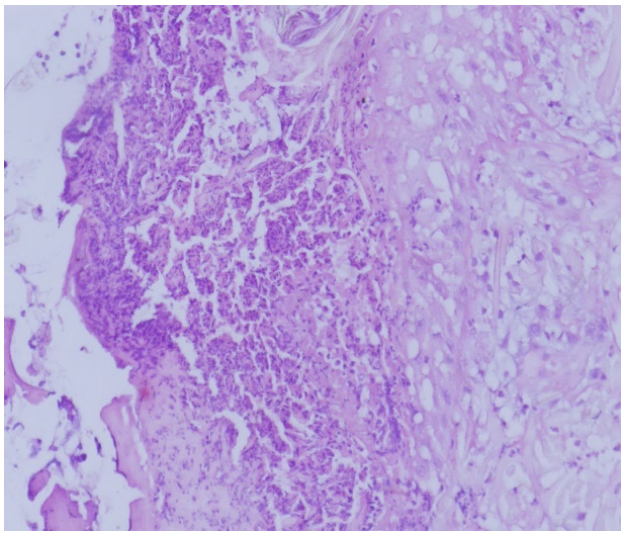
Source: Author's personal collection, 2021.

Figure 1. Macroscopic aspects of the lesions in the dorsal cervical and left scapular regions prior to trichotomy for the diagnostic skin biopsy procedure.



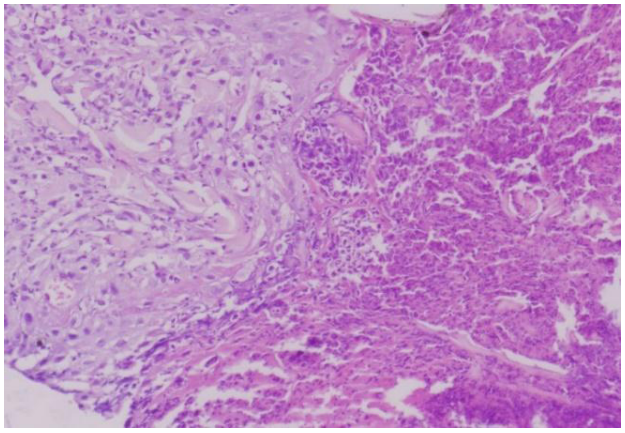
Source: Author's personal collection, 2021.

Figure 2. Alopecic, ulcerated, and exudative lesion in the left scapular region with five weeks of evolution, in addition to alopecic, ulcerated, and exudative lesion with one week of evolution in the dorsal cervical region.



Source: Laboratory of Veterinary Pathology – Federal University of Paraná, Palotina, Brazil, 2021.

Figure 3. Histological section of skin in the cervical region (160X magnification) showing an area of epidermal ulceration (black arrow) and necrosis (red arrow, bottom) covered by inflammatory and necrotic material.



Source: Laboratory of Veterinary Pathology – Federal University of Paraná, Palotina, Brazil, 2021.

Figure 4. Histological section of skin in the cervical region (160X magnification) showing a microabscess (black arrow) and necrotic material on the epidermal surface (red arrow).

along with wound management through cleaning with saline solution and application of a commercial gentamicin-based topical ointment every 12 h. After the appropriate therapeutic institution, the patient showed gradual improvement of the lesions. Up to the present time, the patient has been undergoing treatment and lesion management, with healthy-looking scar tissue and almost complete resolution of the skin lesions.

DISCUSSION

Drug eruption can occur as a result of the administration of any substance. It is more commonly observed following the use of antibiotics (sulfonamides, cephalexin, ampicillin, and the one previously used in the present report, amoxicillin), antihistamines, and methimazole (GROSS et al., 2005). These can trigger mechanisms such as local toxic effects, delayed hypersensitivity reactions—mainly type IV—, cytotoxicity, lymphocytic reactions, and keratinocyte apoptosis (REIMANN et al., 2020).

The initially described lesions were localized and alopecic, evolving to ulcerated and exudative, the largest of which measured 3 cm in diameter, without involvement of the mucosa. These findings corroborate the descriptions by Gross et al. (2005), who characterized the location, alopecia, and ulceration of superficial pustular reactions to medications as clinically variable.

This condition is difficult to diagnose because its clinical signs are nonspecific and its etiology is difficult to prove. Adverse drug reactions should be suspected whenever skin lesions appear following the use of a drug (YOUNG; TORRES; KOCH, 2018). In cases of use of multiple medications, as in the present report, it is extremely difficult to identify which drug or association caused the eruption (LARSSON; LUCAS, 2020).

The clinical presentation must be associated with histopathological examination to rule out differential diagnoses, as the patterns of skin reactions observed in drug allergies can also be observed in other diseases, i.e., in immune-mediated ones such as pemphigus foliaceus and lupus (HNILICA, 2011; VOIE; CAMPBELL; LAVERGNE, 2012).

In the histopathology of the present report, superficial pustulation was observed as a pattern, and the diagnosis was superficial pustular drug eruption. The main differentials are pemphigus foliaceus, superficial pustular bacterial infections (impetigo and superficial pyoderma), and subcorneal pustular dermatosis. Pemphigus foliaceus was excluded due to the absence of acantholysis; the other dermatopathies were ruled out due to the presence of epidermal necrosis (GROSS et al., 2005).

According to the criteria defined by Larsson; Lucas (2020), the reaction described can be characterized as idiosyncratic, since there was an antagonistic situation to the pharmacological action of the administered drugs. As described in this report, the patient had been under drug treatment for two months, after which period skin lesions started to appear.

Idiosyncratic drug toxicity reactions usually occur within the first or second month of drug therapy and are not dose-dependent, although toxicity may increase with increasing dose in susceptible individuals. However, it is not possible to state that the drug eruption occurred due to this specific treatment period, since drug eruption can take place years after the use of the triggering medication (HNILICA, 2011).

Idiosyncratic drug reactions are rare, unpredictable, and unrelated to the pharmacological effect of the substance. Rather, they are related to the individual's immune response or genetic differences in the susceptibility of patients, often being allergic, intolerant, or aberrant reactions (LÓPEZ et al., 2014). Their incidence in dogs and cats corresponds to 2%

and 1.6%, respectively, of all dermatological consultations (MILLER; GRIFFIN; CAMPBELL, 2013).

These reactions may or may not involve an adaptive immune response and, for this reason, the suspected drug must be discontinued and structurally related drugs that may cause a similar adverse reaction should be avoided (TREPANIER, 2013). In humans, clinical signs resolve on average two weeks after interruption of the causative drugs, and to prove which medication is the trigger, it must be administered it again, checking for worsening of clinical signs (REIMANN et al., 2020). In this report, the lesions have not improved thus far, although the patient remained six weeks without any medication. Therefore, we chose to re-administer chlorambucil for therapeutic purposes. Since there was no clinical justification, and for ethical reasons, no other drug re-exposure was performed.

Chlorambucil, an alkylating immunosuppressive drug, has good results in the treatment of pemphigus complex, lupus, and drug eruption, and can be associated with corticosteroids when necessary (MILLER; GRIFFIN; CAMPBELL, 2013). In cases of association, chlorambucil allows corticosteroids to be used sparingly, thus minimizing their adverse effects (JASANI; BOAG; SMITH, 2008). Because clinical improvement was seen only after chlorambucil was added to the treatment protocol for liver disease and inflammatory bowel disease, its use was again instituted, also aiming at its effects on the drug eruption, without associated corticosteroids, to observe the systemic repercussions of the chosen drug. Up to the present time, the patient has been undergoing treatment due to extensive epidermal damage, with gradual and progressive lesion improvement.

CONCLUSIONS

The present report shows the importance of including drug eruption as a differential diagnosis of non-healing lesions in cats, especially in cases where there is a history of use of multiple medications, despite the rarity of the condition. Moreover, it demonstrates the difficulty of resolving the lesions and the severity of microscopic changes, even after the administered medications are discontinued. The study also demonstrates the difficulty of defining the triggering drug, since its administration may have occurred at any time in the animal's life. Because it is an uncommon condition in cats, more reports and studies about its clinicopathological aspects are warranted.

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