



# Case Report of Hemangiopericytoma Development After Prolonged Use of Oclacitinib Maleate in a Dog with Atopic Dermatitis and Iatrogenic Hyperadrenocorticism

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## Case Report

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## Abstract

The canine atopic dermatitis is a chronic allergic disease that affects dogs genetically predisposed. Clinically, dogs present pruritus symptoms that lead to self-trauma. The most commonly used drugs are glucocorticoids to control pruritus, however, due to the genetic nature of the disease, there is a need for continuous and lifelong use of medication, which can lead to the development of iatrogenic hyperadrenocorticism. Therefore, others drugs such as cyclosporine, oclacitinib maleate and lokivetmab are recommended. The oclacitinib maleate is an inhibitor of the intracellular signaling pathway mediated by enzymes of the Janus kinase family, responsible by the activation of T lymphocytes and synthesis of cytokines with pro-inflammatory and pruritic activity and cytokines that participate in survival, development, growth and differentiation of T lymphocytes and cytokines that participate in survival, development, growth and Its use is restricted to dogs with atopic dermatitis that do not present an infectious or tumoral condition. This case report describes a 15-year-old female Lhasa Apso dog initially treated with glucocorticoids who developed iatrogenic hyperadrenocorticism. After replacement with oclacitinib maleate and its prolonged use, the dog presented the growth of three large nodules defined by histological analysis as hemangiopericytoma.

**Keywords:** Hemangiopericytoma; Cutaneous Tumor; Atopic Dermatitis; Oclacitinib Maleate; Adverse Effects

## Abbreviations

JAK: Janus Kinase; ALT: Alanine Aminotransferase; AP: Alkaline Phosphatase.

## Introduction

The canine atopic dermatitis is a chronic inflammatory allergic skin disorder that affects animals with a genetic predisposition, which may present clinical signs between 6 months and 7 years of age, which initially include erythema

and papules. With progression of disease and chronicity of inflammatory process, pustules, macules, crusts, hyperpigmentation, lichenification and alopecia may appear [1].

The classic treatment of canine atopic dermatitis involves the use of glucocorticoids, but their prolonged use can lead to the emergence of iatrogenic hyperadrenocorticism [2]. Therefore, others drugs such as cyclosporine, oclacitinib maleate and lokivetmab are recommended.

Oclacitinib maleate, an inhibitor of enzyme Janus kinase 1 and Janus kinase 2 (JAK1 and JAK2), has recently been introduced to the treatment of canine atopic dermatitis. The Janus kinases belong to a family of non-receptor intracellular tyrosine kinases (JAK1, JAK2, JAK 3 and TYK2) that transduce signals through the JAK-STAT intracellular signaling pathway, which stimulates gene expression of molecules and cytokines that promote leukocyte mobilization, cytokine synthesis and inflammatory response [3].

The oclacitinib maleate inhibits the secretion of cytokines interleukin-2 (IL-2), interleukin-15 (IL-15), interleukin-18 (IL-18), interleukin-31 (IL-31) and interferon gamma (IFN- $\gamma$ ) by helper T lymphocytes, and their associated inflammatory response [4,5]. The most common drug reactions associated with oclacitinib maleate include vomiting and uncomplicated diarrhea; however, long-term treatment may further the development of hyperlipidemia, urinary tract infections and worsening of neoplastic conditions [6,7].

Hemangiopericytoma is a malignant soft tissue tumor of mesenchymal origin of pericytes, which affects the cutaneous and subcutaneous tissue; in dogs, is located mainly in locomotor limbs [8,9]. Its diagnosis is established through histopathological analysis, and its subtypification through

immunohistochemical analysis [10]. This case report describes an association between long-term use of oclacitinib maleate and the development of hemangiopericytoma.

### Case Report

In July 2024, a fifteen-year-old female Lhasa Apso, castrated and vaccinated, was attended. According to the owner, the dog had an atopic allergy since the first two years of life, being initially treated with corticosteroids (prednisolone), and over the years developed iatrogenic hyperadrenocorticism, being treated since then with trilostane (1.5 mg, BID, orally). Due to the pruritic condition associated with atopic dermatitis, the dog began to be treated with oclacitinib maleate (0.6 mg/kg, SID, orally). After four years of continuous treatment with oclacitinib maleate, the dog began to present multiple skin nodules.

During clinical examination, the dog presented an alopecic area in abdomen, hyperpigmentation, hyperkeratosis, lichenification and three large nodules in the skin, located in lower right cervical region, distal end of right pelvic limb and left flank (Figure 1). In addition, the dog had bilateral ocular keratoconjunctivitis sicca.



**Figure 1:** Clinical appearance of female dog with three great skin nodules.

A complete blood count, measurement of alanine aminotransferase (ALT), alkaline phosphatase (AP), glucose, triglycerides, cholesterol, type I urine, dexamethasone suppression test, abdominal ultrasound and doppler echocardiography were performed. A biopsy of the skin nodules was also performed for histopathological analysis.

In the blood count, a smaller number of erythrocytes (5.08 million/mm<sup>3</sup>; normal values=5.7-7.4 million/

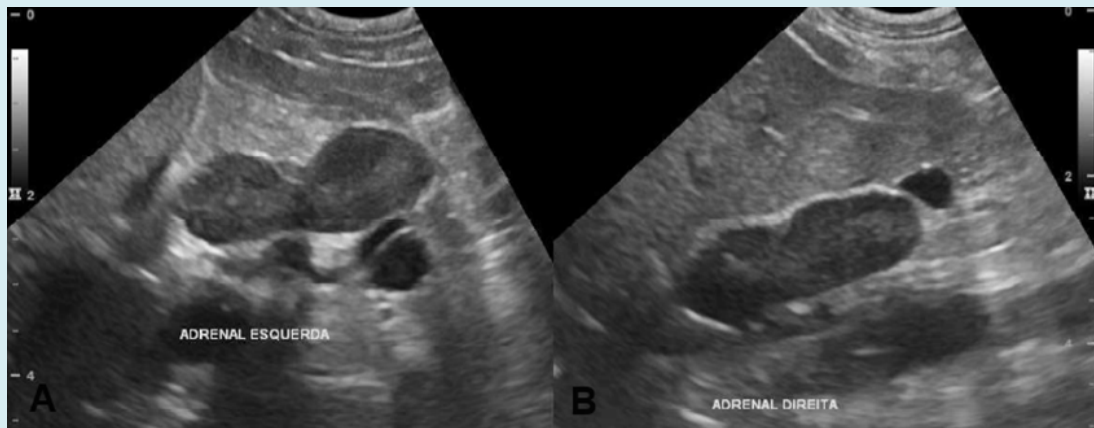
mm<sup>3</sup>), and small decrease in hematocrit (37.0%; normal values=38.0-47.0%) was observed.

The dosages of ALT (252 U/L; normal values=9-92 U/L), AP (350; normal values=10-155 U/L), glucose (155 mg/dL; normal values=60-118 mg/dL), cholesterol (367 mg/dL; normal values=135-270 mg/dL) and triglycerides (292.0; normal values=32.0 a 125.0 mg/dL) were elevated.

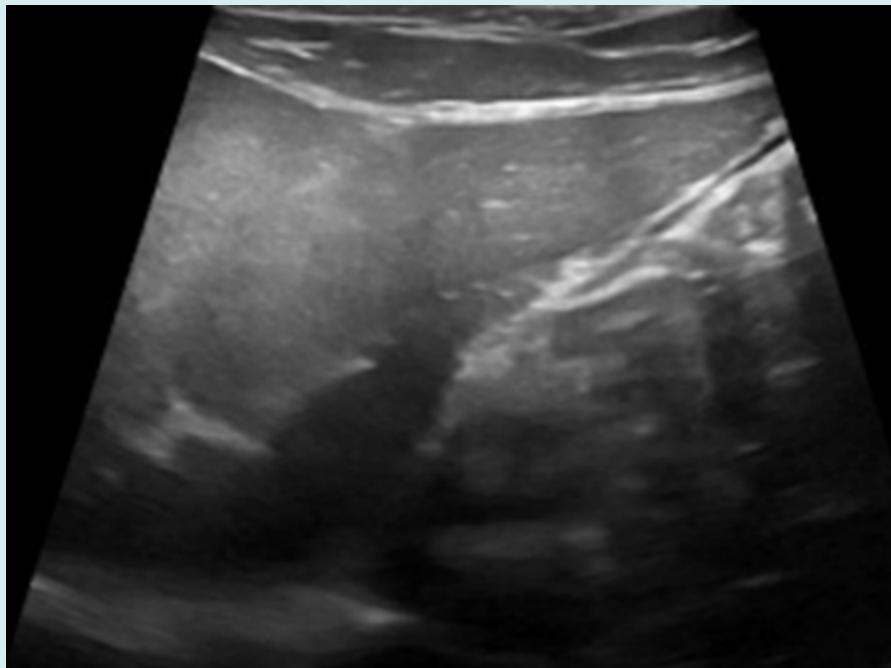
Type I urinalysis was performed by collecting urine through ultrasound-guided cystocentesis, and biochemical examination showed absence of bilirubin, glucose, ketone bodies and occult blood. In sedimentoscopy, erythrocytes, leukocytes and absence of bacteria were observed. In dexamethasone suppression test, the basal cortisol value was 4.45 (normal values= 1.0 a 4.6  $\mu\text{g}/\text{dL}$ ), and the cortisol value 8 hours after dexamethasone was 0.86 (normal value

below 0.90  $\mu\text{g}/\text{dL}$ ). The abdominal ultrasound revealed an increase in the size of adrenal glands and liver (Figures 2 & 3). The doppler echocardiography and color flow mapping not shown any alteration.

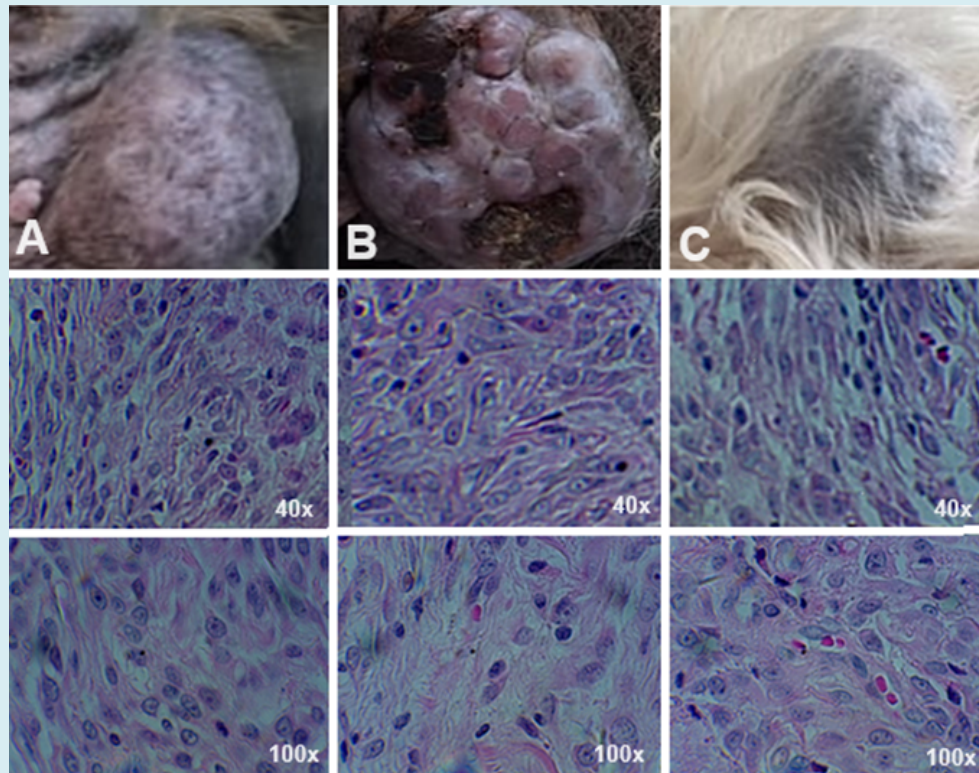
The result of histopathological analysis of samples obtained from the three skin nodules was hemangiopericytoma (Figure 4).



**Figure 2:** Abdominal ultrasound. A. Left adrenal gland with rounded contours and increased dimensions, measuring 2.8 x 1.0 x 0.98 cm (length x thickness of caudal pole x thickness of cranial pole) with reduced echogenicity and preserved echotexture. B. Right adrenal gland with rounded contours and increased dimensions, measuring 2.9 x 1.0 x 0.98 cm (length x thickness of caudal pole x thickness of cranial pole) with reduced echogenicity and preserved echotexture.



**Figure 3:** Abdominal ultrasound. Hepatic lobes with homogeneous parenchyma, rounded contours and diffusely increased echogenicity (chronic liver disease, steroid liver disease or fatty infiltration).



**Figure 4:** Histopathological analysis of the three skin nodules.

The histopathological analysis of the three nodules using a 40 and 100 objective demonstrated the presence of spindle cells in a sarcomatous pattern, with imprecise limits, nuclear pleomorphism and evident nucleoli (hematoxylin/eosin staining). A. Subcutaneous mass located in the distal end of right pelvic limb. B. Nodule located in lower right cervical region formed by multiple small nodules and foci of necrosis. C. Nodule located on left flank.

## Discussion

The canine atopic dermatitis is a genetic disease in which animal is sensitive to allergens present in environment through inhalation, ingestion or contact, being considered a highly pruritic chronic inflammatory disease [1]. The main clinical sign in dogs with canine atopic dermatitis is pruritus, which leads to the appearance of skin lesions caused by trauma, recurrent opportunistic infections and a chronic inflammatory process with thickening of corneal layer (hyperkeratosis), hyperpigmentation, lichenification and alopecia [2]. Animals can develop recurrent and chronic otitis externa, conjunctivitis with secondary blepharitis and keratoconjunctivitis sicca [11,12].

The most commonly used therapy for controlling pruritus involves the use of oral or cutaneous corticosteroids, such as prednisolone and methylprednisolone, that have rapid action and low mineralocorticoid effect. However, due to need for their use for long periods, these medications lead to development of adverse effects that affect liver, adrenal glands

and gastrointestinal tract leading to decrease of quality and longevity life these animals [2]. In the dog of this case study, the problems resulting from prolonged use of corticosteroids were the development of iatrogenic hyperadrenocorticism, with the appearance of bilateral adrenal hyperplasia, anemia, hepatic steatosis and increased serum levels of cholesterol, triglycerides and alkaline phosphatase.

The oclacitinib maleate is a drug used to control pruritus in dogs with canine atopic dermatitis [13,14]. Its mechanism of action involves synthesis blocking of cytokines with pruritic and pro-inflammatory activity, through the inhibition of enzymes from Janus Kinase (JAK) family, such as JAK1 and JAK2 [15].

The oclacitinib maleate has the ability to clinically reduce pruritus, but it does not have the ability to reverse its pathogenesis, requiring continuous use. The protocol indicated for the treatment of atopic dermatitis in dogs uses two cycles, the first through daily administrations with a

12-hour interval for 14 days and the second with a 24-hour interval. Its prolonged use is common in veterinary clinical practice, including the use of daily cycle every 12 hours [16]. In some animals, pruritus returns after changing between cycles by switching to once-daily administration or stopping it [17].

One of the major problems with its continued use is the increased risk of serious infections in animals with an ongoing infection or that have some hidden or present neoplasia. However, the literature does not provide direct evidence of the association between the use of oclacitinib maleate and the development of cancer in dogs [18]. The literature describes the use of oclacitinib maleate associated with depletion of TCD4 and TCD8 lymphocytes in dogs *in vitro*, of T and B lymphocytes in lymphoid tissues in a murine experimental model, and decreased in lymphoproliferative activity and cytokine synthesis (IFN- $\gamma$ , IL-2 and IL-15), factors that contribute to reduce the ability of immune system to control the growth of tumor cells [19-21]. The drug's leaflet warns about its action on the immune system and its promotion of tumor progression. In the dog in this case study, a diagnosis of hemangiopericytoma was made, a tumor originating from pericytes (cells that surround the capillaries) with slow growth [8,9]. It was suggested by tutor that prolonged use of oclacitinib maleate was the emergence cause of hemangiopericytoma, but he was unable to inform whether the animal had any lesions prior to the use of this drug. Since the dog presented continuous use of glucocorticoids and hyperadrenocorticism, also capable of causing immunosuppression, it was not possible to establish a plausible association regarding the emergence of hemangiopericytoma.

## Conclusion

The canine atopic dermatitis is a skin disease that affects dogs with a genetic predisposition mainly to aeroallergens. Due to the appearance of pruritus and self-trauma, treatment involves drugs that modulate the immune response, such as glucocorticoids. Since its long-term use can lead to the emergence of iatrogenic hyperadrenocorticism, other drugs have been developed, such as oclacitinib maleate. Although this drug is capable of controlling the pruritic condition, it interferes with the immunosurveillance system, favoring the progression of already established tumors. Therefore, it is essential that the veterinarian is alert about its use in animals with canine atopic dermatitis.

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