CASE REPORT

Adenoma of the *pars intermedia* of the pituitary gland in a horse in Colombia, morphological and immunohistochemical study: case report

Adenoma de la pars intermedia de la hipófisis en un caballo en Colombia, estudio morfológico e inmunohistoquímico: reporte de caso

Adenoma da pars intermedia da glândula pituitária em cavalo na Colômbia, estudo morfológico e imuno-histoquímico: relato de caso

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Abstract

Anamnesis: An Argentine saddle horse with poor body condition, general weakness, and recurrent pathological decubitus without response to treatment was euthanized and subjected to diagnosis. **Clinical and laboratory findings:** At necropsy, hirsutism, and poor body condition were observed. The pituitary gland protruded from the sella turcica and measured 2.3 cm thick and 2.8 cm high. A nodule measuring 1.3 cm in diameter was observed in the *pars intermedia* of the pituitary gland. Histological findings revealed an adenoma in the *pars intermedia* of the pituitary gland. The neoplastic cells were immunoreactive for ACTH, and the markers for PRL, NSE, and GFAP were negative. The ultrastructure of the neoplastic cells showed intracytoplasmic granules of variable electron density and diameters between 160 and 250 nm. **Conclusion:** This is the first report of a *pars intermedia* adenoma in an Argentine saddle horse and the first comprehensive diagnosis of this neoplasia in Colombia and South America.

Keywords: *ACTH; Argentine saddle horse; Colombia; equine; gelded male; neoplasia; pituitary.*

Resumen

Anamnesis: Un caballo Silla Argentina con mala condición corporal, debilidad y decúbito patológico sin respuesta al tratamiento fue sacrificado y sometido a diagnóstico. **Hallazgos clínicos y de laboratorio:** En la necropsia se observó hirsutismo y mala condición corporal. La glándula pituitaria protruyó de la silla turca y medía 2,3 cm de grosor y 2,8 cm de alto. En la *pars intermedia* de la hipófisis fue observado un nódulo de 1,3 cm de diámetro. En histopatología se reveló un adenoma en la *pars intermedia* de la glándula pituitaria. Las células neoplásicas fueron inmunorreactivas para ACTH, los marcadores para PRL, NSE y GFAP fueron negativos. La ultraestructura de las células neoplásicas mostró gránulos intracitoplasmáticos de densidad electrónica variable y diámetros entre 160 y 250 nm. **Conclusión:** Este es el primer reporte de un

adenoma de *pars intermedia* en un caballo Silla Argentina y el primer diagnóstico integral de esta neoplasia en Colombia y Sudamérica.

Palabras clave: *ACTH; caballo Silla Argentina; Colombia; equino; macho castrado; neoplasia; pituitaria.*

Resumo

Anamnese: Um cavalo Sela Argentino com condição corporal magro, fraqueza geral, decúbito patológico recorrente e sem resposta ao tratamento, foi eutanasiado e submetido ao diagnóstico. **Achados clínicos e laboratoriais**: Na necropsia foram observados pelos arrepiados e condição corporal ruim. A glândula pituitária tinha 2,3 cm de espessura e 2,8 cm de altura e projetava-se da sela túrcica. Na *pars intermedia* da glândula pituitária observou-se um nódulo de 1,3 cm de diâmetro. A histopatologia revelou um adenoma na *pars intermedia* da glândula pituitária. As células neoplásicas foram imunorreativas a ACTH e os marcadores de PRL, NSE e GFAP foram negativos. Na ultraestrutura das células neoplásicas observaram-se grânulos intracitoplasmáticos de densidade eletrônica variável e diâmetros entre 160 e 250 nm. **Conclusão**: Este é o primeiro relato de um adenoma na *pars intermedia* em um cavalo Sela Argentino e o primeiro diagnóstico abrangente desta neoplasia na Colômbia e na América do Sul.

Palavras-chave: *ACTH; cavalo de Sela Argentino; Colômbia; equino; macho castrado; neoplasia; hipófise.*

Introduction

The adenoma of the *pars intermedia* (PI) of the pituitary gland is a frequent reported neoplasm in horses (Miller *et al., 2016*). The location of PI adenoma hamper its surgical approach, and it is usually a cause of death or leads to compassionate euthanasia (Miller *et al*., 2016). When the adenoma is an endocrinologically active neoplasm, it is one of the recognized causes of the condition known as pituitary *pars intermedia* dysfunction (PPID) (Kirkwood *et al*., 2022). Degenerative diseases of the hypothalamic neurons contributes to loss of dopaminergic inhibition and it is a risk factor for neoplasms of the *pars intermedia* (Fortin *et al*., 2021; Gris *et al.,* 2023) producing proopiomelanocortin (POMC) and its derivatives, followed by growth alterations in

cells in the PI of the pituitary that protrude and compress the hypothalamus (McFarlane, 2007, 2011; Miller *et al*., 2016). The cause of neuronal degeneration is unknown; however, it was proposed that accumulation of misfolded alpha-synuclein may lead to such degeneration and hypothalamic compression; a mechanism similar to that described in Parkinson's disease (Fortin *et al*., 2021). Other authors propose excess production of POMC causing hyperplasia, hypertrophy, or adenomas in the PI (McFarlane, 2011; Fortin *et al*., 2021).

Immunohistochemistry (IHC) studies in equine endocrine neoplasia are scarce, immunostaining of PI adenoma is usually positive and strong for POMC, β-endorphin (β-END), α-melanocyte stimulating hormone (MSH) and adrenocorticotropic hormone (ACTH) (Boujon *et al*., 1993; Meuten, 2017). Ultrastructural studies of neoplastic cells identify secretory granules, well-developed endoplasmic reticulum, and accumulation of filaments and other organelles (Boujon *et al*., 1993).

To the authors' knowledge, there are no reports of pituitary adenomas in horses in Colombia and PI adenoma has not been described in Argentine saddle horses. Therefore, the aim of this study was to describe an adenoma of the PI of the pituitary in a Argentine saddle horse in Colombia, through a comprehensive study of the macroscopic lesions, optical microscopy, IHC and transmission electron microscopy (TEM).

Case presentation

Anamnesis

A horse was found in sternal recumbency and unable to stand in a paddock located in the Bogotá Savannah (North latitude 4,653, West longitude 74,097). The veterinarian reported that the horse showed similar recurrent clinical signs over a period of approximately two years. As time went by, the episodes became more frequent and the pathological prostration became longer, the deterioration of the horse's health worsened in the last three months. The horses grazed *Cenchrus clandestinum* (Kikuyu grass), supplemented with two rations of 1.5 kg per day of commercial feed for adult horses (Campeón® concentrate), mineralized salt and water *ad libitum*. Only one affected animal was found in a batch of 57 horses in total.

Clinical findings and diagnostic aids used

The veterinarian reported that the clinical examination of the Argentine saddle breed horse, a 32-year-old gelding, revealed general body weakness, lethargy, and inability to stand. Phenylbutazone® IM 4.4 mg/kg, SID, was administered, but there was no response to the treatment. Due to the animal's deterioration in recent months and the poor prognosis, the horse was euthanized out of compassion. The body was sent for veterinary diagnosis to the Laboratorio de Patología Veterinaria de la Universidad Nacional de Colombia (LPV-UNAL).

At the necropsy, the animal had a poor body condition based on obvious bony protuberances, severe diffuse muscle atrophy, scarce subcutaneous, mesenteric, and coronary sulcus adipose reserves. The palpebral and conjunctival mucosa were pale and moderately jaundiced. The presence of a long non shedding hair coat was interpreted as hypertrichosis (hirsutism) (Fig. 1a), thin fragments of whitish flaking material of different sizes and shapes were noted within the hair coat (dandruff). The pituitary gland was found enlarged and it protruded from the sella turcica (Fig. 1b). The size of the pituitary gland was 2.3 cm thick and 2.8 cm high with nodular areas. In the sagittal section, yellow nodules with brown foci were observed in the middle region. The diameter of the largest nodule was 1.3 cm (Fig. 1c). The coronary, mesenteric and omental fat was scant, gelatinous in appearance, brownish yellow in color and translucent (reminiscent of adipose tissue serous atrophy). The thyroid glands showed moderate hypertrophy and lobular appearance, when cut, abundant content of mucous appearance and black color was discharged. Samples of the pituitary gland, skin, thyroid gland, intestine, liver, and adrenal glands were collected for histology and fixed in buffered formalin (pH 7) for 48 h, for subsequent routine histological processing using the Hematoxylin and Eosin technique (H&E).

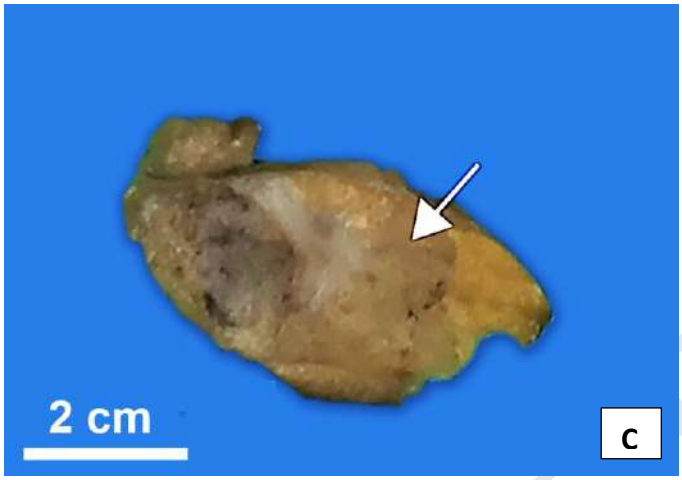


Figure 1.A. Argentine saddle horse with adenoma of the *pars intermedia*. The horse was in poor body condition and hirsutism. **B.** Exposed pituitary gland in the cranial cavity. The enlarged pituitary gland presented nodules of firm consistency that protruded from the sella turcica (arrow). **C.** Sagittal section of the pituitary gland. The middle region of the pituitary revealed well-defined yellow nodules with brown spots, which displaced adjacent tissues (arrow) and altered the anatomical surface.

Microscopically, the PI of the pituitary gland had a partially encapsulated growth pattern that displaced and compressed the *pars distalis* and the neurohypophysis. The neoplastic cells were arranged in multiple nodules, cords and nests in 60% of the neoplasm (Fig. 2a), in 30% they formed pseudorosettes (radiated growth or palisade around blood vessels) (Fig. 2b) and 10% of the cells were organized around a colloidal-looking fluid content, arranged as thyroid follicle-like structures of different sizes and shapes with random distribution (Fig. 2c). The neoplastic cells were predominantly round, polyhedral and few spindle-shaped. The cytoplasm was granular, large, eosinophilic, micro vacuolated, and some cells were binucleated. There was mild anisocytosis, mild pleomorphism, mild cytomegaly with indistinguishable cell borders. The nuclei were large chromatic found in a central or parabasal position, round, oval and few with angular edges. Some nuclei showed mild pleomorphism, with cleft nuclei, few aberrant nuclei, mild anisokaryosis, mild karyomegaly, some vesiculated nuclei, fine granular chromatin, a prominent nucleolus, or two small nucleoli. Four mitoses were observed in 2.37 mm^2.

Severe diffuse epidermal atrophy and hyperplasia of hair follicles without sebaceous glands were observed in the skin, most of them in the anagen phase and few in the catagen phase. Brain base neurons revealed central chromatolysis, perineural edema, neuronal retraction, and moderate

satellitosis. In the adrenal gland, moderate diffuse cortical hyperplasia with hyperplastic capsule nodules. In the intestinal tract, mild diffuse neutrophilic fibrinous necrotic enterocolitis, few pseudomembranes, and multiple bacterial colonies with intralesional coccobacilli morphology were observed. In the liver, severe, active chronic random, multifocal pyogranulomatous hepatitis with portal fibrosis and subacute severe diffuse suppurative cholangiohepatitis was observed.

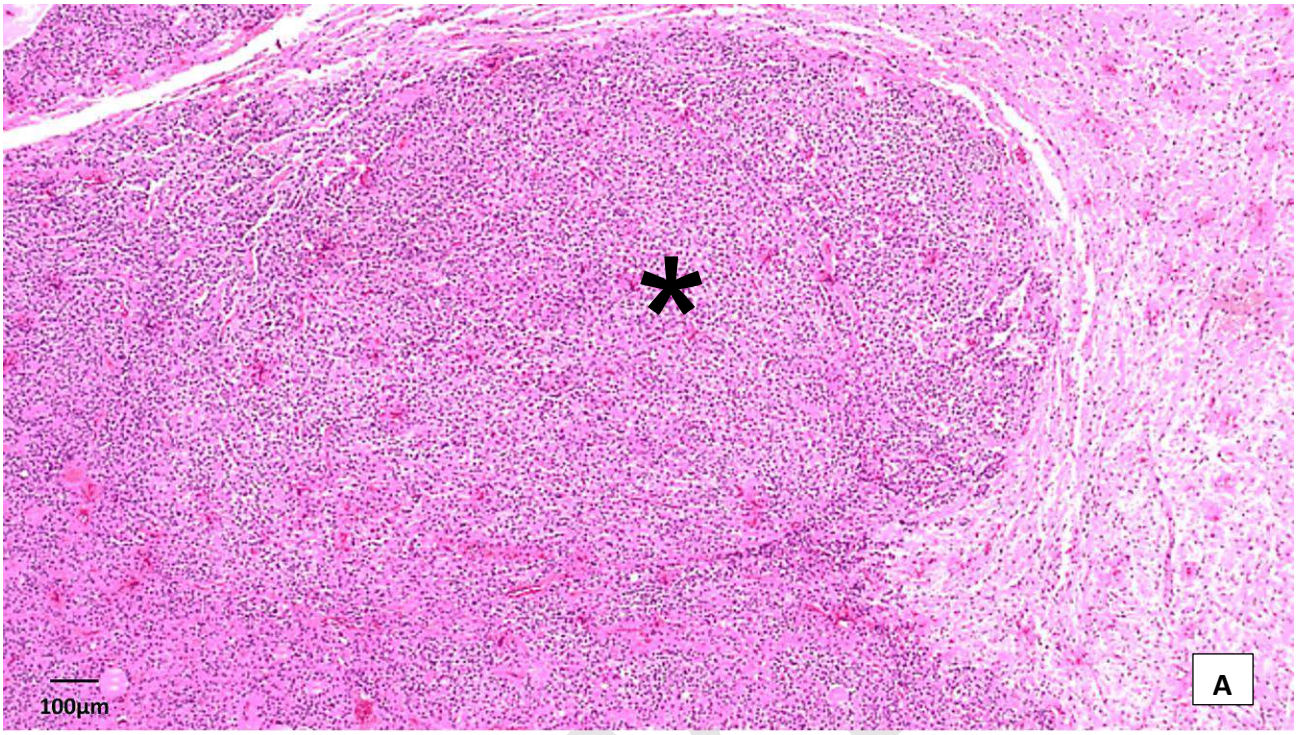
Sequential sections for IHC studies were made from the pituitary paraffin blocks. The tissues were deparaffinized and incubated with specific antibodies for the detection of pituitary hormones, followed by a HRP conjugated polymer detection. The IHC procedures were performed by the company INMUNOTECH®. The analysis was done by a trained veterinary pathologist from LPV-UNAL. The criteria for IHC evaluation were those described in the literature (Boujon *et al*., 1993) with some modifications: 1) negative, without labeling. 2) Positive, when it revealed granular intracytoplasmic and/or perinuclear immunostaining, it was established as weak positive when the intensity of the immunostaining was weak in a population < 20% of the neoplastic cells, moderate between 20% - 50% and strong when the intensity of the immunostaining was strong and well defined in a proportion > 50% of the neoplastic cells; each antibody had a positive control.

Neoplastic cells of the pituitary PI revealed strong ACTH-positive intracytoplasmic and perinuclear granular immunostaining (Fig. 2D) even in foci of satellite neoplastic cells that had infiltrated the *pars distalis*. Markers for prolactin (PRL), glial fibrillary acidic protein (GFAP) and neuronal specific enolase (NSE) in pituitary, were negative (Table 1).

Table.1 Primary antibodies used for immunohistochemical study of *pars intermedia* neoplasia.

Antibodies	Clon	Dilution	Species produced	Antigen retrieval method	Detection kit
ACTH	O2A3	1:800	Mouse	HIER*	HRP conjugated polymer
GFAP	GA5	1:2000	Mouse	HIER	HRP conjugated polymer
NSE	MRQ-55	1:120	Mouse	HIER	HRP conjugated polymer
PROLACTIN	EP193	RTU**	Mouse	HIER	HRP conjugated polymer

*HIER: Heat-induced epitope retrieval; **RTU; ready to use.



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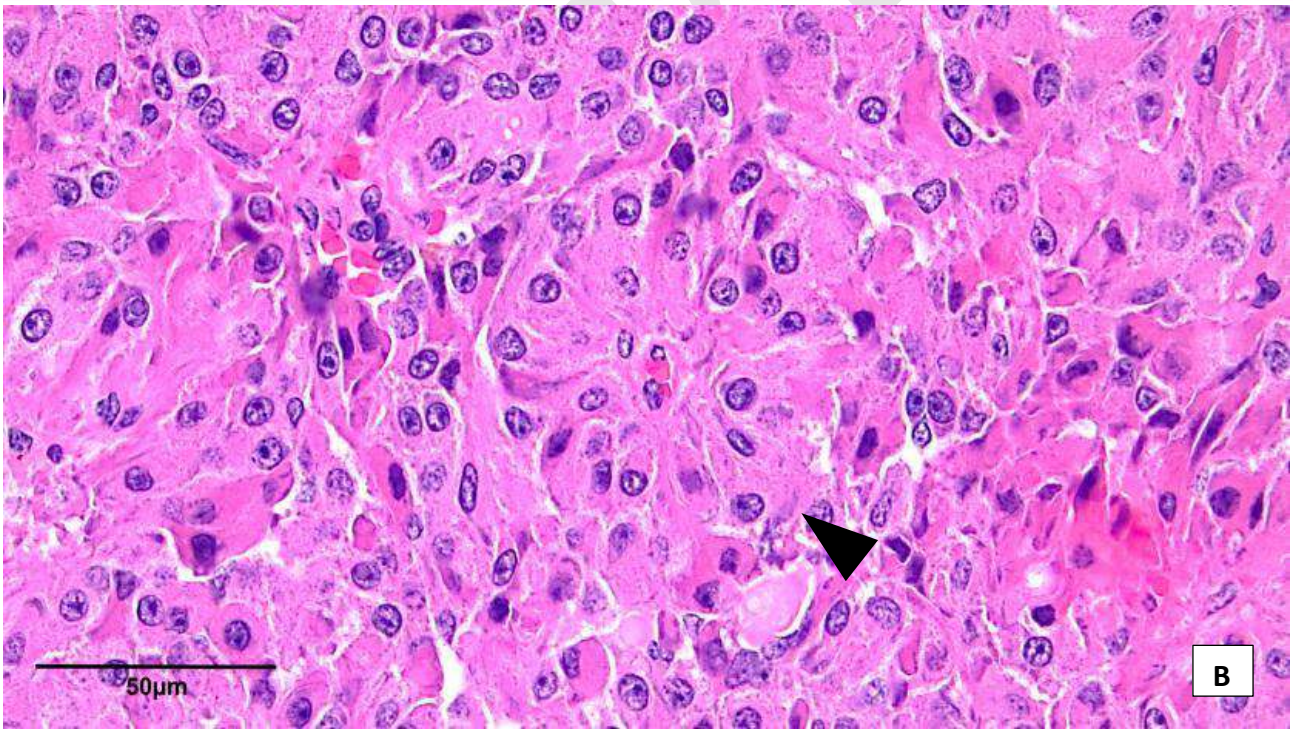

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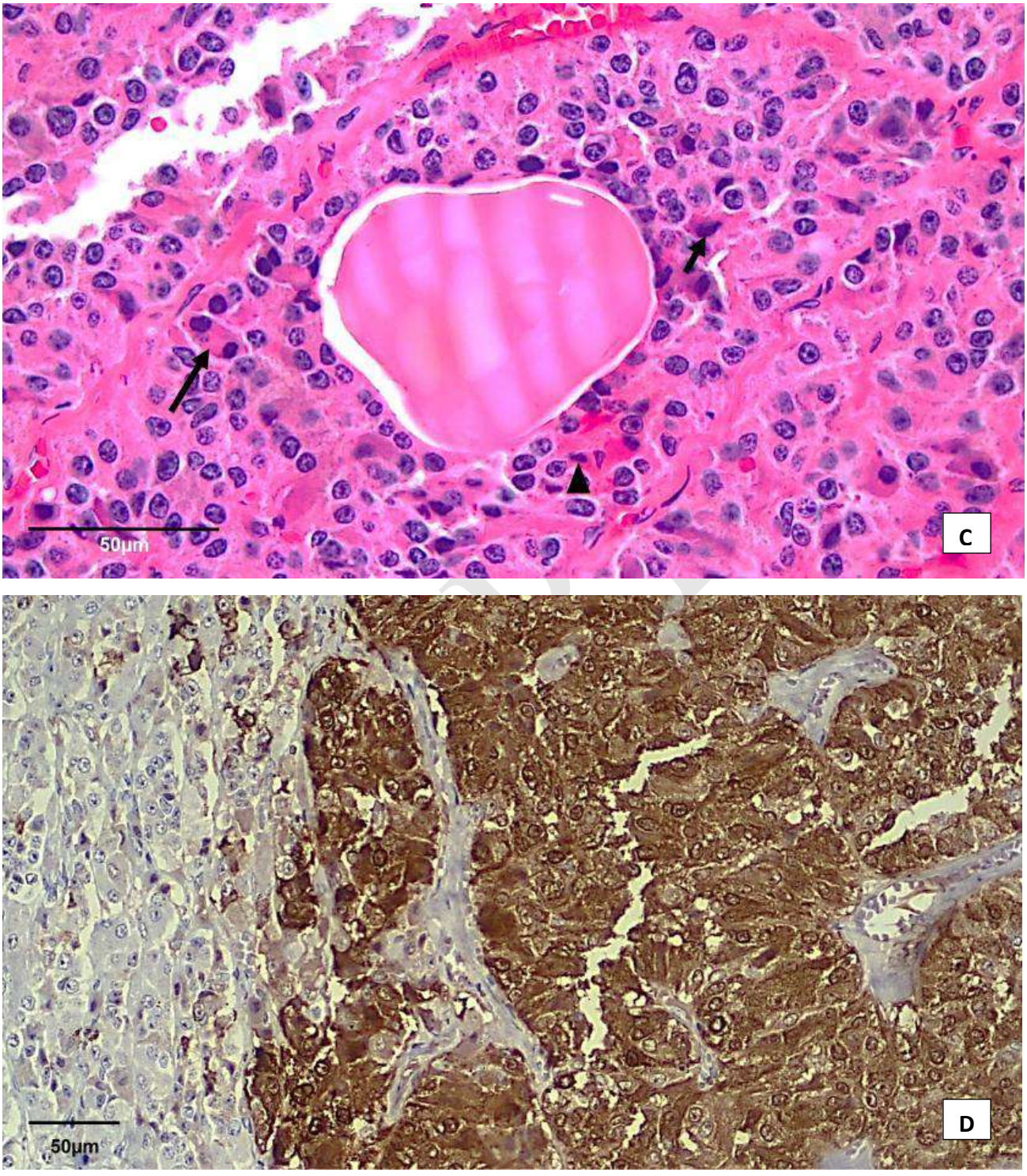

Figure 2. A. *Pars intermedia* adenoma of the pituitary gland in a horse. Two adjacent nodules of proliferating neoplastic cells of the *pars intermedia* was observed. The neoplastic cells are organized in cords or nests delimited by fine connective tissue and capillaries. The neoplastic nodules (asterisk) protrude, compress and displace the neurohypophysis located at the right side.

H&E. x100. **B.** Palisade cells was observed around blood vessels forming pseudorosettes (arrowhead). H&E.x400. **C.** The growth pattern of the neoplastic cells were organized as thyroid follicle-like structures with accumulation of secreted proteinaceous colloid material. Binucleated cells (long arrow), amorphous nuclei (short arrow) and mitotic figure (arrowhead). H&E.x400. **D.** Intracytoplasmic and perinuclear immunostaining for ACTH of the neoplastic cells. IHC x200.

A nodule of the pituitary *pars intermedia* neoplasm was preserved in glutaraldehyde buffered in 2.5% PBS for 24 h. Samples were subsequently fixed in 1% osmium tetroxide (1 h) and processed for electron microscopy. Ultrastructural analysis revealed neoplastic cells with cytoplasmic granules of variable electron densities and with diameters between 160-250 nm. Multiple mitochondria, smooth endoplasmic reticulum, and well-developed rough endoplasmic reticulum were observed. The neoplastic cells showed round or oval nuclei with shallow indentations and some with prominent nucleoli. Mild anisokaryosis, abundant euchromatin diffusely distributed in the nucleus and heterochromatin attached to the nuclear membrane were noted (Fig. 3).

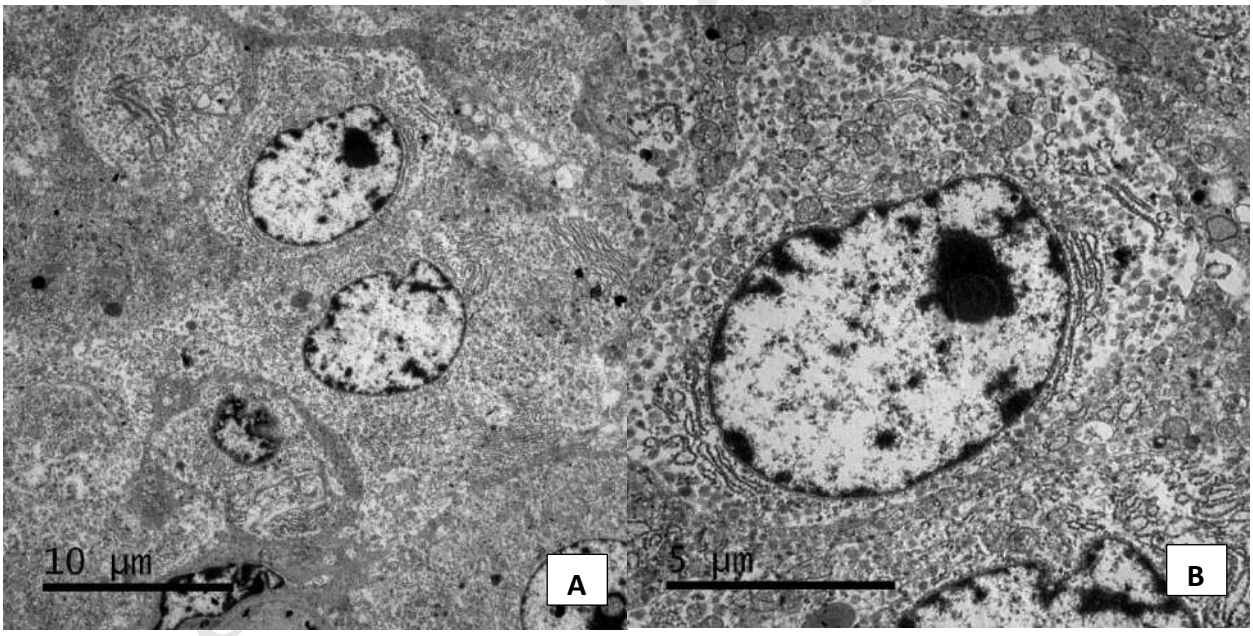

Figure 3. Ultrastructure evaluation of the adenoma of the *pars intermedia*. A. Polyhedral, oval or cubic cells with irregular cytoplasmic borders; cleft nuclei; Abundant randomly distributed secretory granules of different electron densities in the cytoplasm. TEM. B. High magnification detailing the secretory granules, multiple mitochondria, well-developed rough endoplasmic reticulum with abundant ribosomes. TEM.

Discussion

An Argentine saddle horse presented clinical signs that included poor body condition, chronic body weakness and recurrent pathological decubitus. The necropsy revealed an enlarged pituitary gland, severe hirsutism, and severe diffuse muscle atrophy. Light microscopy, IHC and TEM confirmed the presence of morphological changes that are observed in cases of ACTH-producing PI adenoma of horses. The morbidity was 1.8% (1/57) and mortality was 1.8% (1/57). This neoplasm occurs sporadically. The clinical signs in the case presented here were similar to those reported in other horses with ACTH-producing PI adenomas (Boujon *et al*., 1993; Yoshikawa *et al*., 2001; Gris *et al*., 2023).

The pituitary gland protruded from the sella turcica and the height of the gland was 2.8 cm. This macroscopic finding suggested an adenoma of the pituitary gland. Miller *et al*. (2008) described adenomas of the pituitary gland in four horses, in which the average height of the pituitary glands was greater than 1.6 cm. According to criteria for histological classification of pituitary gland lesions in horses, which include grades from 1 to 5, pituitary lesions with a diameter > 0.5 cm are classified as grade 5 and correspond to adenomas (Miller *et al*., 2008). Thus, the histological lesion in the pituitary gland of this case was classified as a grade 5 adenoma.

The morphological patterns of the neoplasia described here were similar to those reported in other PI adenomas (Miller *et al*., 2008; Meuten, 2017). The cellular morphology of neoplastic cells and highly homogeneous nuclear size correspond to that described by others (Boujon *et al*., 1993; Yoshikawa *et al*., 2001; Meuten, 2017). In addition, at least four mitotic figures were counted in 2.37mm^2., some binucleated cells, mild megalocytosis, mild megalokaryosis and few aberrant nuclei were also found.

Morphological findings in the skin are described in hormonal dermatosis (Meuten, 2017) and in horses with PPID (Spelta, 2015; Gris *et al*., 2023). However, the mechanism behind those changes is unknown; overproduction of POMC and a consequent increase in ACTH that influences follicular development in the anagen phase has been suggested (Morgan *et al*., 2018). Strong immunodetection of ACTH hormone in the neoplastic cells of PI adenoma explains the skin lesions. However, this needs to be confirmed by serum ACTH levels.

Histologically, necrotic, neutrophilic, fibrinous enterocolitis with intralesional bacteria. This finding represents an acute infection. In addition to pyogranulomatous hepatitis was found. Both events might be explained by subclinical bacterial and/or parasitic infections although microbiology and parasitology were not conducted in this study. McFarlane *et al*. (2015) described frequent secondary infections in PI adenomas and hypothesize that they are a consequence of the loss of regulation of the immune system or the influence of increased levels of ACTH. We hypothesize that the animal had immunosuppression due to the neoplasia.

The ultrastructural findings of the neoplastic cells were like those described for tumors with secretory activity (Horvath and Kovacs, 1976). In the case presented here, granules with a diameter between 160-250 nm were found, they also appeared in different stages of secretion, which is like those described for ACTH containing secretory granules (Boujon *et al*., 1993; Yoshikawa *et al.*, 2001; Osamura *et al*., 2008).

The rough endoplasmic reticulum and Golgi apparatus were well developed with abundant mitochondria; such findings were like those described in ACTH-producing PI adenomas (Boujon *et al*., 1993). However, TEM revealed multifocal secretory activity, which might alter the visualization of granules and their electron density (Mete *et al*., 2016). It is recommended caution when analyzing neoplasms of the pituitary gland in horses using TEM alone and the diagnosis should be done on the basis and findings obtained with other diagnostic tests such as IHC (Yoshikawa *et al*., 2001; Mete *et al*., 2016). In this case, the ultrastructural findings obtained by TEM were complemented with positive intracytoplasmic immunostaining for ACTH using IHC, supporting the diagnosis of adenoma of the PI in a horse.

Pituitary PI neoplasia has been described in several horse breeds (Boujon *et al*., 1993; Yoshikawa *et al*., 2001; Miller *et al*., 2016; Gris *et al*., 2023). However, according to the authors' knowledge, this neoplasia has not been described in Argentine saddle horses and horses raised in Colombia. For this reason, this study constitutes the first report of pituitary PI neoplasia in this horse breed and contributes to the available information on the disease in horses. Few reports of pituitary gland neoplasia that include a comprehensive morphological study and confirmation using IHC and TEM are available in the literature. In conclusion, this is the first comprehensive study describing a

pituitary PI adenoma with electronic and light microscopy, and inmunohistochemistry in a horse in Colombia and South America, and the first in the Argentine saddle horse breed.

Declarations

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Conflicts of interest

The authors declare they have no conflicts of interest with regard to the work presented in this report.

Author contributions

Necropsy, histopathology, literature review and writing of the first manuscript: DGG and BDD. IHC, TEM and critical revision of the manuscript: PCEC and BDD. All authors reviewed and approved the final version.

Use of AI

No AI or AI-assisted technologies were used during the preparation of this work.

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