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Granular cell tumor in the central nervous system of a ferret (*Mustela putorius furo*) - a case report

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ABSTRACT

A granular cell tumor (GCT) in the central nervous system (CNS) of a ferret is a rare finding. In this case a cerebral GCT is described in a 5-year-old castrated female ferret. The animal developed lameness in right hind leg which progreseed to total ataxia. The animal died and a necropsy revealed the mass in the medial to caudal part of the left frontal lobe of the brain. Based on histological and imunohistochemical findings, tumor was diagnosed as granular cell tumor. Immunohistochemically, granular cells were diffusely positive for vimentin and neuron-specific enolase (NSE) and weakly focal reactivity for S-100 protein was seen. Neoplastic cells did not express cytokeratins and glial fibrillary acidic protein (GFAP). Although immunohistochemistry was performed, histogenesis of this tumor remains unsolved and controversial.

Key words: brain; granular cell tumor; ferret (*Mustela putorius furo*); histopathology; immunohistochemistry

Introduction

Granular cell tumours (GCTs) encompass a histologically heterogenous group of tumors which reflects the still unsolved histogenesis of these tumors. The name of these tumors is descriptive and does not imply a certain cell of origin or line differentiation (PATNAIK, 1993). These tumors are characterized by an abundance of intracytoplasmic granules, whose nature and function still remain unclear (MACHADO et al., 2016) They are usually benign but may exhibit aggressive behavior with local and distant reccurences (NASSER et al., 2010; AKAHANE et al., 2015; MACHADO et al., 2016).

Granular cell tumors have been reported in different animal species occuring both within the nervous system and extraneurally (PATNAIK, 1993; MIYAJIMA et al., 2001; WILLIAMS and WYRE, 2020). In the CNS, GCTs have been described in the rat (YOSHIDA et al., 1997), dog (HIGGINS et al., 2017), cat (MANDARA et al., 2006) and one ferret (SLEEMAN et al., 1996). One other case of GCT in a ferret has been reported in the literature

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but it has not been described in detail (WILLIAMS and WEISS, 2004). Despite immunocytochemical studies, histogenesis of these cells remains unsolved and controversial. Hystiocytes (SHEAR, 1960), smooth muscle cells and Schwann cells (SOBEL et al., 1971), fibroblasts (APARICIO and LUMSDEN, 1969), and pluripotential mesenchymal cells (TURK and BREEZE, 1981) have been proposed as precursors of granular cells. In the rat, the GCT is the most common primary CNS tumor and it is thought that these tumors may have derived from meningeal arachnoid cells (YOSHIDA et al., 1997). Similarly, HIGGINS et al. (2001) also suggested these tumors in dogs originate from leptomeninges and indicate the tumors are not of pituicyte, oligodendroglial or astrocytic derivation (since they were negative for GFAP), which is common in humans (VIZCAINO et al., 2019). Results of ultrastructural and IHC analysis have led to the general acceptance that GCT have their origin in Schwann cells or that they have neuroendocrine origin (WILSON, 2017). Furthermore, it has been suggested that GCT are caused by degeneration of different cells rather than chromosomal imbalances (HIGGINS et al., 2001). For example, PÉREZ et al. (2005) suggested that granular cells in their study represent meningothelial components with degenerative changes. Newer research in human GCTs suggested that they could be a result of inactivating somatic mutations in the endosomal pH regulators ATP6AP1 or ATP6AP2 resulting in impaired vesicle acidification, redistribution of endosomal compartments and accumulation of intracytoplasmic granules (PAREJA et al., 2018). In this research this was shown to be true in 72% of studied GCTs from different locations, excluding the CNS.

To the authors knowledge, only one report of GCT in a ferret has been reported in scientific literature (SLEEMAN et al., 1996). In that study, a case of GCT in the CNS of a ferret (*Mustela putorius furo*) was described, but immunohistochemistry wasn't performed. The clinical behavior, prognosis, and paraneoplastic syndromes in ferrets are often far different from what is seen with similar neoplasms in dogs or cats, thus extrapolating diagnostic and therapeutic options from comparable syndromes in more traditional pet species can be problematic (WILLIAMS and WYRE, 2020). Here, we described clinical and histopathologic findings including immunohistochemistry of GCT in the CNS of the ferret.

Case history

A 5-year-old castrated female ferret was temporarily put in care without clinical signs of disease. A routine health check was done beforehand. The level of troponins was slightly elevated. A heart ultrasound, ECG and X-ray were performed, but the cause could not be found. Other biochemical and haematological parametres were within the normal range. After three weeks the animal showed lameness on right hind leg which progresed and it became totally ataxic. The animal developed inappetence and incontinence. It was treated with Sucralfat and Meloxoral. Despite this therapy, the animal died two days later. A necropsy was performed and tissue samples of the brain with tumor mass and other parenchymal organs were collected, fixed in buffered 10% formalin and submitted for histopathological examination. Paraffin-embedded samples of the brain were stained with haematoxylin and eosin (HE) and periodic acid Schiff (PAS). To identify the histogenesis of this tumor, immunohistochemical staining was perfomed using a streptavidin-biotin peroxidase method. Primary antibodies used in this case are shown in Table 1.

Table 1. Used primary antibodies

Antigen	Antibody	Antibody dilution	Cod	Source
vimentin	monoclonal	1:100	M 0725	Dako
cytokeratin	monoclonal	1:60	M 3515	Dako
S-100 Protein	polyclonal	1:400	Z 0311	Dako
GFAP	monoclonal	1:50	M 0761	Dako
NSE	monoclonal	1:200	M 0873	Dako

At necropsy, major changes were seen in the brain, and other parenchymal organs were congested. In the medial to caudal part of the left frontal lobe there was a 14x15 mm whitish-gray, friable, expansive, well demarcated, unencapsulated mass that compressed adjacent brain tissue and expanded toward subependimal areas of the lateral ventricule (Fig.1).

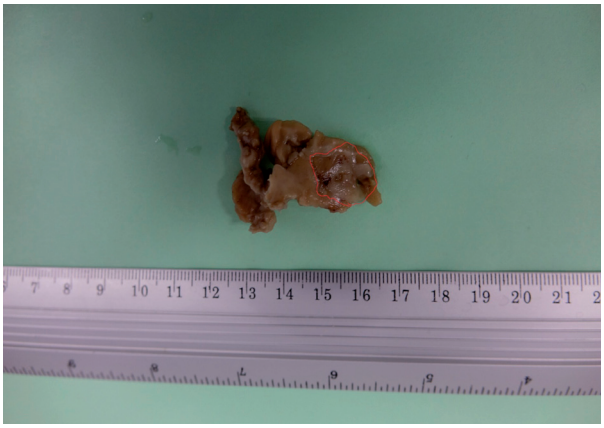

Fig.1. Brain, ferret: gross appearance of a granular cell tumor in left frontal lobe (a cut section). Formaline fixed tissue, tumor marked by red line

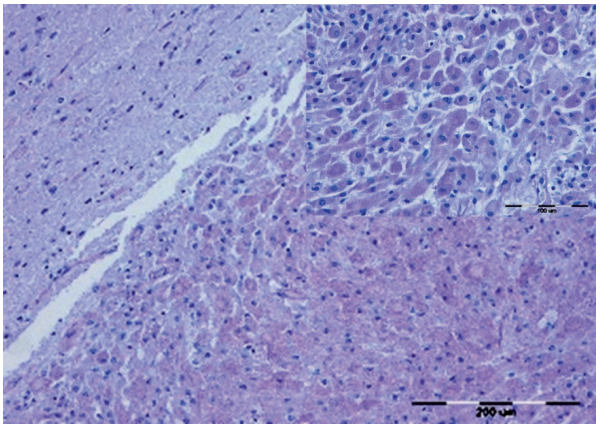

Fig. 3. Brain, ferret: intracytoplasmic periodic-acid Schiff (PAS) positive granules. PAS, x 200, inset x 400

Histopathologically, the tumor was composed of sheets and nests of large round to poligonal cells admixed with a few spindle shaped cells supported by a sparse fibrovascular stroma. Neoplastic cells were characterized by abundant granular pale eosinophilic cytoplasm and round nuclei with stippled chromatin and a single central nucleolus. Mitotic figures were rare. Centrally within the mass there were areas of necroses and haemorrhage (Fig. 2). The tumor cells granules were variably PAS-positive (Fig. 3).

Immunohistochemically, the granular neoplastic cells were diffusely and strongly vimentin (Fig. 4) and NSE (Neuron Specific Enolase) positive (Fig. 5), but showed weak positive reactivity to S-100 protein (Fig. 6). Neoplastic cells did not express cytokeratin AE1/AE3 and GFAP (not shown). Based on histopathology and IHC, the tumor was diagnosed as granular cell tumor.

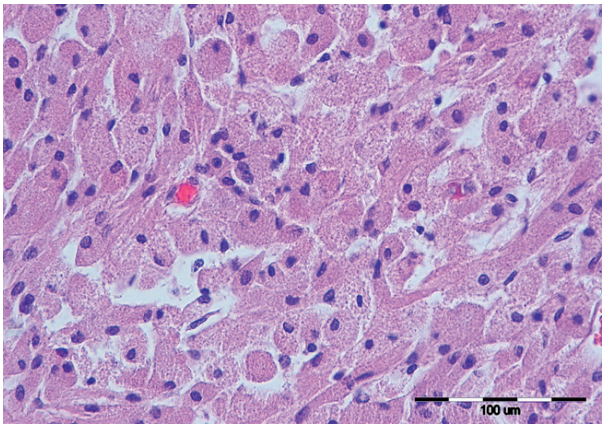

Fig. 2. Brain, ferret: microscopic appearance of GCT: large round to polygonal tumor cells with abundant granular eosinophilic cytoplasm admixed with few spindle shaped cells. HE, x 200

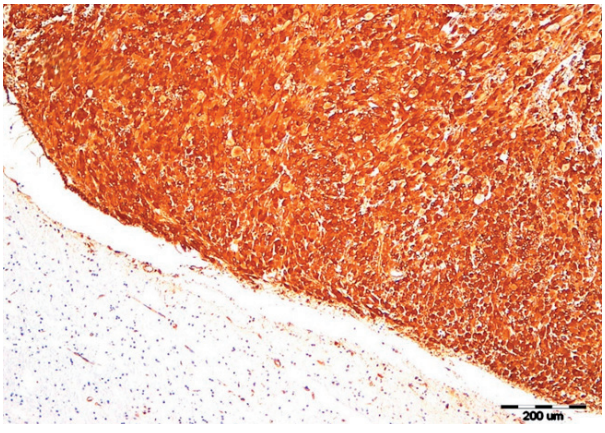

Fig. 4. Brain, ferret: the granular cytoplasm of all neoplastic cells is strongly diffusely positive for vimentin. IHC, vimentin, x 100

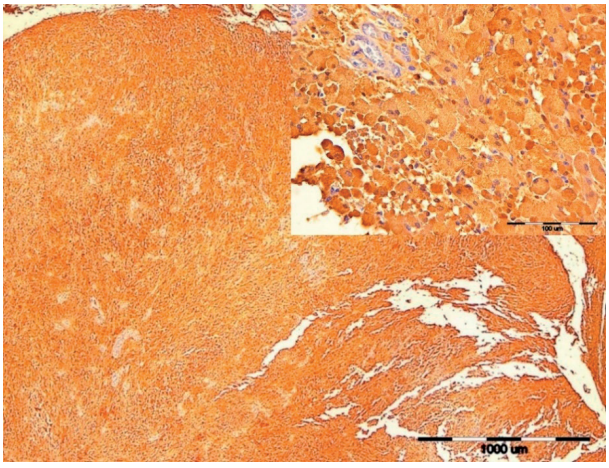

Fig 5. Brain, ferret: diffuse strong intracytolasmatic expression of neuron-specific enolase (NSE) in GCT. IHC, NSE, x100; inset x200

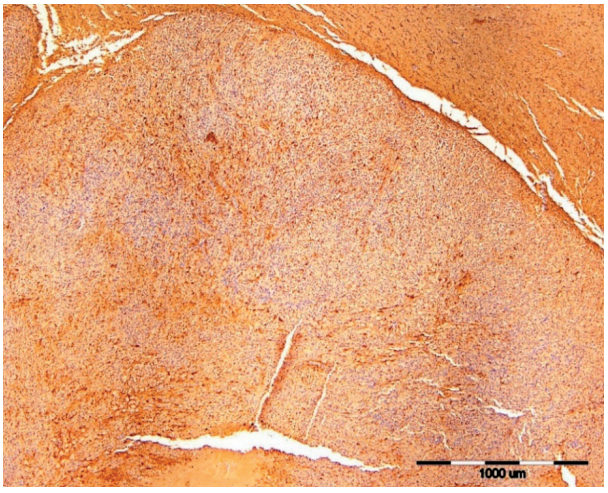

Fig. 6. Brain, ferret: neoplastic cells demonstrate weak positive reactivity to S-100 protein. IHC, S-100, x100

Discussion

Neoplasia is a common cause of disease in domestic ferrets worldwide and the most common neoplasms are islet cell tumors (insulinoma), adrenocortical neoplasms, and lymphoma (WILLIAMS and WYRE, 2020). Neoplasms of the nervous system are rare, accounting for less than 0,5% of reported tumors in ferrets (WILLIAMS and WEISS, 2004.). Primary tumors of the CNS in ferrets include astrocytoma (ANTINOFF and WILLIAMS, 2012), granular cell tumor (SLEEMAN et al., 1996), choroid plexus papilloma (VAN ZEELAND, 2009), meningioma (MIWA et al., 2009) and embryonal tumor (DIAS et al., 2019). Primary tumors of the brain and spinal cord usually result in severe neurologic deficits over time, as was the case with the ferret in this study. Central nervous system tumors are the third most common cause of neurological signs in ferrets (ANTINOFF and WILLIAMS, 2012), after insulinoma and bacterial meningitis/encephalitis (VAN ZEELAND et al., 2009; ANTINOFF and WILLIAMS, 2012). Primary neurologic diseases are uncommon in pet ferrets (POWERS and BROWN, 2012; MANCINELLI, 2015) and clinical signs are often a manifestation of systemic illness rather than primary neurological disease (POWERS and BROWN, 2012; MANCINELLI, 2015). Thus, accurate case assessment and diagnosis of neurological problems in this species is often challenging for the veterinary practitioner (MANCINELLI, 2015). Clinical signs associated with tumors in nervous system are quite variable and often nonspecific (DIAS-FIGUEROA and SMITH 2007; ANTINOFF and WILLIAMS, 2012). They can include ataxia, lateralizing signs, cranial nerve deficits, uncontrolled seizure activity, and normocellular cerebrospinal fluid, in the presence of a normal blood glucose level. Tumors of the CNS generally lead to development of neurological signs, including head tilt, circling, ataxia and seizures, whereas those of the peripheral nervous system result in body-surface masses that owners usually notice before any neurological signs develop (HUYNH and PIAZZA, 2021).

To the authors knowledge this is the second histopathologically described case of a GCT in CNS in ferrets. Gross and histopathological findings were similar to those first described in the ferret by SLEEMAN et al. (1996), and in other animal species (PATNAIK, 1993; YOSHIDA et al., 1997; MIYAJIMA et al., 2001; MANDARA et al., 2006; HIGGINS et al., 2017; WILLIAMS and WYRE, 2020). Also, in our case the cytoplasmic granules of tumor cells were positive for PAS staining, which is in agreement with results reported by the abovementioned authors. On the other hand, the GCT cells were PAS negative in one case of a dog with atypical meningeal GCT (MISHRA et al., 2012).

Immunohistochemical analysis in the present case showed that tumors cells were diffusely strongly positive for vimentin, which points to a mesenchymal cell origin. Previous research on GCT in different locations showed different results regarding vimentin staining. For instance, GEYER et al. (1992) studied GCT in a horse, a cat and dogs, where only samples from two dogs with tongue and palate tumors showed positive vimentin staining. In a study of PATNAIK (1993) all samples, except from the tumor in bird, were vimentin positive. HIGGINS et al. (2001) described variable positive staining for vimentin in two dogs with GCT in the brain. Authors who described GCT in dogs, all reported positive vimentin staining (LIU et al., 2004; PÉREZ et al., 2005; MISHRA et al. 2012), whereas MIYAJIMA et al. (2001) reported negative vimentin staining in nine mice with GCT.

Neoplastic granular cells in our study also stained positive for NSE, suggesting neuronal origin. Positive NSE staining was also found in a lung GCT in a horse (PATNAIK, 1993), two dog GCT (LIU et al 2004; RAO et al., 2010), and NSE staining was also positive, although with less intensitiy, in a dog orbital meningioma with a granular cell component (PÉREZ et al., 2005). On the other hand, GEYER et al. (1992) reported strong positive NSE staining in the horse and dogs, but negative NSE staining in the cat sample. In the same study, in cases of two dogs, positive NSE accompanied by positive vimentin staining suggests a mesenchymal origin, and not neuroectodermal/Schwann cell origin since the cells showed negative staining for S-100 protein, GFAP, desmin and cytokeratin. GEYER et al. (1992), claimed that NSE seems to be less valuable as the indicator for neuronal differentiation because it is not a reliable indicator of a neural origin of these tumors. MIYAJIMA et al. (2001) reported negative NSE staining for all nine mice with GCT. MISHRA et al. (2012) reported negative NSE staining for an atypical meningeal GCT in a dog CNS, which, combined with negative S-100 does not support the idea of neuronal origin.

The tumor cells in our research were positive for S-100, although with less intensity. Weaker S-100 reactivity was also found in two dogs with GCT on the tongue and the palate (GEYER et al., 1992), two dogs with brain GCT (HIGGINS et al., 2001), and a dog with an orbital meningioma (PÉREZ et al., 2005). S-100 positivity was found in a dog with meningioma and a lung GCT in a horse (PATNAIK, 1993), suggesting a neural origin of the tumor. Similar results of immunolabeling with S-100 were described by RAO et al. (2010) in a dog with GCT in the lumbar spinal nerve, which, in combination with NSE staining, suggests neuronal origin of the tumor. LIU et al., 2004 reported positive S-100 staining of tumor cells from an intracranial GCT in a dog. Negative S-100 staining was found in mice with GCT (MIYAJIMA et al., 2001) and a dog with atypical meningeal GCT (MISHRA et al., 2012).

In our case the tumor cells did not express cytokeratins, which excludes possible epithelial origin of tumor cells, or glial fibrillary acidic protein (GFAP), which excludes astrocytic origin. This is in congruence with findings in dogs with GCT in the CNS (HIGGINS et al., 2001) and orbital meningioma with a granular cell component (PÉREZ et al., 2005). Similar findings were found in dogs, a horse and a bird (PATNAIK, 1993) and a GCT in the CNS of a cat (MANDARA et al., 2006). Positive cytokeratin staining was only found in two dogs with ear and lip GCT (GEYER et al., 1992), and all other published research showed negative GFAP staining (GEYER et al., 1992; MIYAJIMA et al., 2001; PÉREZ et al., 2005; MISHRA et al., 2012; HIGGINS et al., 2017)

There is strong evidence that a uniform histogenesis of domestic animal GCTs does not exist. For example, HIGGINS et al. (2001) excluded leucocyte origin of tumors immunohistochemicaly and they suggested meningeal cell origin and not of pituicyte, oligodendroglial or astrocytic derivation as in most of the human CNS tumors (MARKESBERRY et al., 1973; FRIEDE and YASARGIL, 1997; RICKERT et al., 1997). Immunohistochemical analysis performed by MANDARA et al. (2006) revealed that granular neoplastic cells of cerebral GCT in a cat were diffusely and strongly vimentin positive, while they didn't express cytokeratins, lysozyme, and synaptophysin, and based on morphologic and immunohistochemical findings the tumor was considered to be meningeal arising. Authors think

that tumor arose directly from meninges or from meningeal elements scattered in the thela choroidea of the third ventricule roof. MITSUMORI et al. (1987) described a review of 107 rat meningeal tumors in which a transition from meningothelial meningiomas to granular cell tumors was identified in 21 of 26 cases, suggesting that all rat meningeal tumors might be related and derived from an arachnoidal cell precursor. An electron microscopic study performed by YOSHIDA et al. (1997) supports this conclusion. HIGGINS (2017) quotes that granular cell tumors in the CNS are most common in the cerebral meninges of the dog but are rare in the cat. When compared to above mentioned studies with similar immunohistochemical findings, a meningeal origin of tumor cells can be considered a possibility. Despite immunohistochemical studies, histogenesis of these cells seems to remain unsolved and controversial.

In conclusion, although rare, granular cell tumors (GCTs) should be considered a differential diagnosis in ferrets with neurologic symptoms. Despite many theories about their origin, the histogenesis of these tumor cells is still uncertain. Recent studies in human GCTs suggest mutations as a possible cause, but these hypotheses should be extended to CNS tumor studies as well. Hovewer, this possibility should also be taken into consideration in animal GCTs.

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SAŽETAK

Granularni stanični tumor u središnjem živčanom sustavu tvora (*Mustela putorius furo*) rijetka je pojava, a ovom radu opisan je kod pet godina stare ženke. Životinja je razvila šepavost stražnje desne noge koja je prerasla u potpunu ataksiju. Nakon uginuća napravljena je obdukcija kojom je otkrivena masa u medijalnom do kaudalnom dijelu lijevog frontalnog režnja mozga. Na temelju histološkog i imunohistokemijskog nalaza, tumor je dijagnosticiran kao granularni stanični tumor. Imunohistokemijski su u ovom slučaju tumorske stanice bile difuzno pozitivne na vimentin i neuron-specifičnu enolazu (NSE), a uočena je slaba fokalna reaktivnost na S-100 protein. Neoplastične stanice nisu eksprimirale citokeratine i glialni fibrilarni kiseli protein (GFAP). Iako je napravljena imunohistokemijska analiza, histogeneza ovog tumora ostaje neutvrđena i kontroverzna.

Ključne riječi: mozak; granularni stanični tumor; tvor (*Mustela putorius furo*); histopatologija; imunohistokemija