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Case report

EPENDYMAL CYST IN THE CAUDAL CRANIAL FOSSA OF A YOUNG BELGIAN MALINOIS DOG WITH ABNORMAL CEREBROSPINAL FLUID FINDINGS

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Fluid-filled cavities within the brain are well-recognized in human and veterinary medicine. Congenital or acquired brain cystic lesions could be isolated or associated with other diseases. Clinical signs related to cysts depend on their size and the mass effect they exert on surrounding neuroanatomical structures. We present a case of a 5-month-old Belgian Malinois dog with cervical pain and right head tilt. The dog had a normal haematochemical profile and negative infectious disease tests. A contrast enhancement Computed Tomography scan revealed the presence of a thin-walled cystic lesion in the caudal cranial fossa at the level of the right pontine-cerebellar junction. A cerebrospinal fluid tap was performed by lumbar puncture, revealing a monocytic pleocytosis. After initial improvement following corticosteroid and antibiotic therapy, clinical signs worsened, and the dog underwent a second clinical evaluation and magnetic resonance imaging examination. After euthanasia a complete postmortem examination was performed. Histological and immunohistochemical findings were suggestive of an ependymal cyst.

Keywords: aseptic meningitis, brain anomaly, congenital anomaly, ependymal cyst, intracranial cyst, working dog

INTRODUCTION

Fluid-filled lesions within the brain are well described pathological findings in people and animals [1]. Cystic lesions can be divided in congenital or developmental and acquired, secondary to or associated with inflammatory and neoplastic intracranial disease. Cyst-related clinical signs depend on the size and location of the lesion and

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the mass effect they exert. These lesions could be asymptomatic and their finding might be incidental [2,3].

Generally, intracranial cysts are described as lesions with an epithelial lining, filled with fluid. Congenital cerebrospinal fluid-filled cavities include hidranencephaly and porencephaly, intracranial intra-arachnoid diverticula, epidermoid and dermoid cyst, Rathke's cleft cyst, ependymal cyst, and choroid plexus cyst.

Ependymal cysts are extremely rare in dogs and to the authors' knowledge only one case report in a dog has been published [4]. The origin of ependymal cysts remains unsure, but it seems that they develop during embryogenesis subsequent to sequestration of developing neuroectoderm [5].

CASE PRESENTATION

A 5-month-old male entire Belgian Malinois was admitted to "Petcare Veterinary Clinic" with two-day history of neck stiffness, cervical pain and right head tilt. The subject was a working dog, and he had started his training at three months of age, showing no signs of ataxia, pain, and motor or balance deficits. The reported syndrome was new for the hitherto normal subject. The dog was referred for a clinical and imaging evaluation. He was treated with low-dose corticosteroid and antibiotic (amoxicillin-clavulanic acid) therapy for five days, with mild clinical signs improvement.

On presentation, the dog was bright and alert, and had an unremarkable general physical examination. A right head tilt, marked neck stiffness and vestibular ataxia were identified at neurological examination. Pain was elicited on gentle palpation of the neck. Proprioception on four limbs, and cranial and spinal nerves examination were normal. Based on clinical findings, a multifocal lesion (vestibular syndrome and cervical myelopathy) was suspected. Differential diagnosis included inflammatory and congenital diseases; a vascular or neoplastic aetiology was considered less likely, due to the signalment and the onset of clinical signs. Complete blood cell count and biochemistry profile revealed no abnormalities. Ehrlichia, Toxoplasma, and Neospora tests were negative. All the procedures were carried out with the written consent of the owner.

Pre and post contrast Computed Tomography (CT) scan of head and neck was performed. A non-ionic iodinated contrast medium Ioversolo (Optiray 300 mg/mL Guerbet Cedex, France) at a dose of 600mg/kg was used. The CT was performed with a 16 slice multidetector CT (GE Optima 540, Waukesha, WI, USA).

For the CT scan evaluation, the dog was premedicated with 0.2 mg/Kg methadone (Semfortan 10mg/mL, Dechra Eurovet Animal Health B.V. - Netherland) and 4 mcg/Kg dexmedetomidine (Dexdomitor 0.5 mg/mL Vetoquinol, Italy). Anesthesia was induced by intravenous administration of propofol 4 mg/Kg (PropoVet 10mg/mL Zoetis Roma, Italy) and, after endotracheal intubation, maintained by administration of isoflurane (Vetflurane, Virbac SA, Carros, France) and oxygen.

The CT revealed a thin-walled cystic lesion (3.8 x 3 x 3.5 cm) in the caudal fossa at the level of the right pontine-cerebellar junction. The lesion showed fluid content (HU 1-12) and mild peripheral contrast enhancement. This cyst expanded caudally in the caudal cranial fossa, causing a severe mass effect, displacing the cerebellum dorso-laterally and compressing the brainstem ventrally and to the left (Figures. 1-2). The cyst slightly protruded through the foramen magnum to the cranio-medullary junction progressing into the vertebral canal and extending dorsally to the compressed spinal cord. Mild asymmetrical fluid sleeve around the spinal cord was recognizable at the level of the proximal third of C2. A mild ventriculomegaly with minimal periventricular hypoattenuating halo was noted.

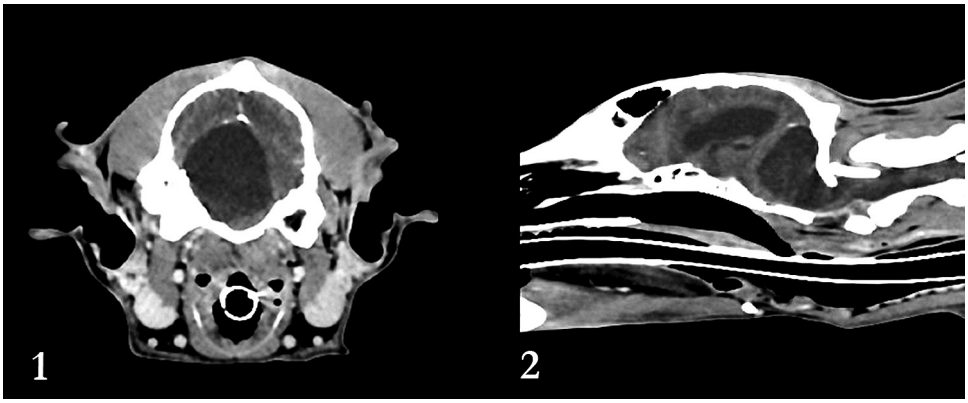


Figure 1. Post contrast CT transverse image of the skull at the level of the right pontine-cerebellar junction. The thin-walled cystic lesion (3.8 x 3 x 3.5 cm) occupies the caudal cranial fossa, showing a fluid content (HU 1-12) and mild peripheral contrast enhancement.

Figure 2. Post contrast CT midsagittal image of the brain. The cyst expanded caudally in the caudal cranial fossa, causing severe mass effect and compressing the brainstem ventrally.

Cerebrospinal fluid (CSF) tap was performed by lumbar puncture. CSF protein content was above normal ranges (0.45 g/litre) as white blood cell count (30 cells/microlitre); cytological examination revealed a monocytic pleocytosis. The diagnosis was consistent with caudal cranial fossa congenital cyst; the abnormal CSF findings could be explained with a concurrent inflammatory condition (i.e. meningoencephalitis of unknown origin MUO, steroid responsive meningoarteritis) or could be related to the congenital abnormality. High-dose prednisolone (Prednicortone tablets 20 mg, Dechra, Northwich, UK - 2 mg/kg) was started and the antibiotic therapy (Clavaseptin tablets, 250 mg, Vetoquinol, Forlì-Cesena, Italy) at a dose of 22mg/kg was continued waiting for pending laboratory results. In the following days, a significant clinical improvement was reported by the owner (i.e. resolution of neck pain and stiffness, and only a residual head tilt).

After an initial improvement, the clinical condition worsened. Two weeks later, the neurological examination revealed a left head tilt, contralateral to the first

presentation, vestibular ataxia, and cervical stiffness. Proprioception on four limbs, and cranial and spinal nerves examination were normal. No pain was elicited at gentle spine palpation. The deduced neurolocalization was left cerebellum-brainstem (i.e paradoxical vestibular syndrome) based on clinical deficits at that time and previous imaging findings. A magnetic resonance imaging (MRI) (Hitachi airis light 0.22 T) of the cervical spine and brain were performed under general anaesthesia. A large and rounded fluid-filled cavitary lesion (signal intensity similar to the CSF: markedly hyperintense on T2W sequences, completely suppressed in FLAIR, hypointense on T1W and absence of signal void areas on GRE sequences) occupied the caudal cranial fossa, almost entirely replacing the right cerebellar hemisphere and vermis and severely displacing and compressing the left cerebellar hemisphere (Figure 3). Likewise, the brainstem was ventrally compressed and displaced to the left. Minimal, linear and peripheral contrast uptake after administration of paramagnetic contrast agent was detected (Prohance, Gadoteridolum, 0.5mmol/ml, Bracco, Milan, Italy). At the level of the left cerebellopontine angle with extension in near proximity of the cochlea, an apparently linear hyperintensity was observed, with signal suppression in FLAIR sequence, hypointense with moderate peripheral focal contrast uptake on T1W (Figure 4). A moderate ventriculomegaly was also evident. The C1-T5 spinal cord MRI was

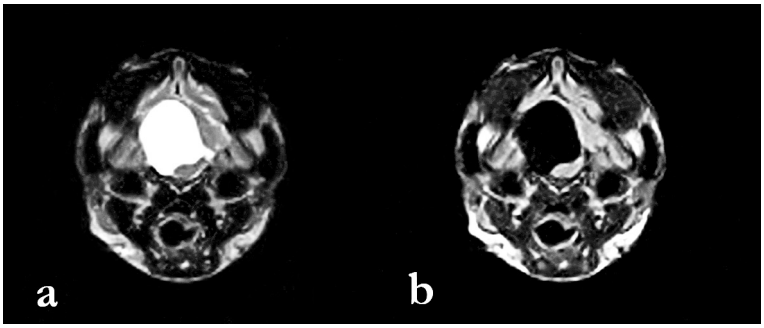


Figure 3 Transverse T2W **(A)** and FLAIR **(B)** MRI images of the brain at the level of cerebellar-pontine angle. T2W hyperintense content is completely suppressed in FLAIR sequence (B)

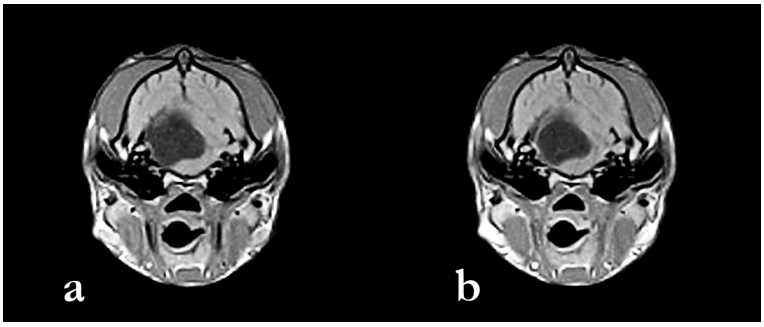


Figure 4 Transverse pre (A) and post contrast (B) T1W images of the brain at the level of the tympanic bullae. Minimal, linear perilesional contrast enhancement after administration of paramagnetic contrast agent.

unremarkable. Based on imaging findings the cystic congenital malformation in the caudal cranial fossa was confirmed, without any concurrent intracranial lesions, other than equivocal minimal linear and peripheral contrast uptake.

Approximately twenty days after the MRI and without any clinical improvement despite the ongoing therapy, the dog was euthanized on request of the owner. A post-mortem examination was performed shortly after euthanasia. No gross lesions were observed, except after disarticulation of the atlanto-occipital joint where a large cyst was observed protruding from the foramen magnum and compressing the medulla oblongata (Fig. 5). This cyst was covered by meninges and lined with a thin transparent wall which collapsed after the brain was removed, releasing clear and transparent fluid like normal cerebrospinal fluid. The cyst replaced most of the left side of the caudal cranial fossa and markedly compressed the left cerebellar hemisphere and displaced the vermis. The continuity with the rhomboid fossa was evident and the fourth ventricle was not dilated. Mild symmetrical dilation of the lateral ventricles was observed. The whole brain was fixed in 4% buffered formalin for 10 days. Representative specimens of the entire brain were embedded in paraffin and cut at 4 μm for histopathologic and immunohistochemical examination. Sections for histopathology were stained with hematoxylin and eosin (HE). Immunohistochemistry was performed with a monoclonal mouse anti-cytokeratins (1:200, clone AE1/AE3, DAKO M3515, Glostrup, Denmark) and polyclonal rabbit anti-glial fibrillary acidic protein (GFAP; 1:100, DAKO Z0034, Glostrup, Denmark) (Fig. 6). Sections were dewaxed, rehydrated, and treated with hydrogen peroxide 3% in distilled water for 30 minutes to eliminate endogenous peroxidase activity. For antigen retrieval, sections were treated by water bath in citric acid buffer, pH 6.0 at 80°C for 2 hours. To prevent unspecific reactions, tissue

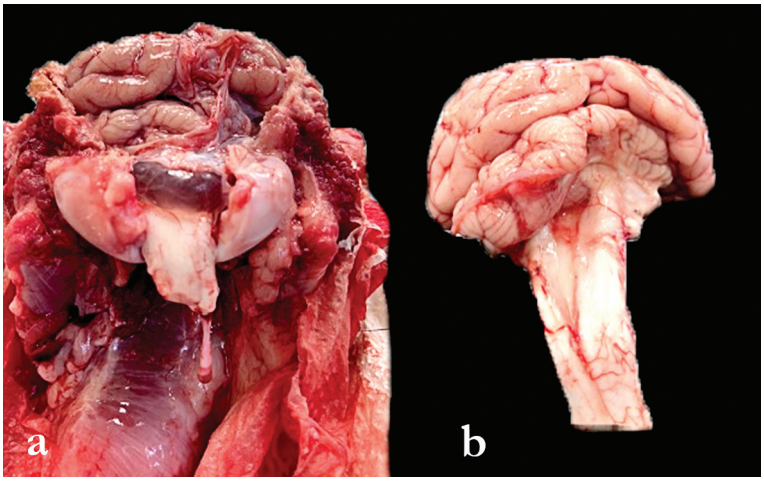


Figure 5 Dorsocaudal aspect of the brain after removal from the skull **(A)** and after removal of the calvarium **(B)**. Left image, the large cyst is protruding the foramen magnum. The cyst had a transparent and thin wall. On the right, the cyst collapsed after it was removed from the caudal fossa, compressed the right cerebellar hemisphere and displace the vermis.

sections were blocked with bovine serum albumin (5%) in TBS for 20 minutes and normal horse serum (5%) in TBS for 20 minutes. Sections were then incubated with primary antibodies at 4°C overnight. Staining was visualized by the polymer-based system VECTOR, ImmPRESS^{TM} detection kit, M-7500 producing a brown color at the site of the reaction. In negative control sections, the primary antibody was substituted with an irrelevant antibody (rabbit IgG). A transversal section of canine duodenum as positive control for cytokeratin were also included. Histologically, the cystic cavity appeared lined by a folded membrane composed of a single thin layer, rarely double, of cuboidal or flattened ependyma-like cells with apical cilia (Fig. 6). The cyst was focally covered by a morphologically normal arachnoid membrane. The cyst wall cells showed clear immunohistochemical positivity for GFAP, while they were cytokeratin negative. GFAP-positive ependymal cells were also observed ventrally and medially, covering the remaining cerebellar parenchyma. Within the cerebellar folia bordering the cyst, the cortex appeared thin and rarefied due to loss of Purkinje cells and marked reduction in the density of the granule cell layer. Other areas of the brain were unremarkable. The overall morphological and histological features of the lesion was consistent with an ependymal cyst.

The cervical spinal cord was not submitted for histological examination.

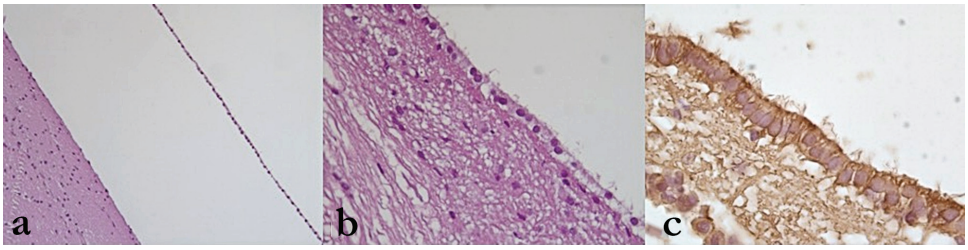
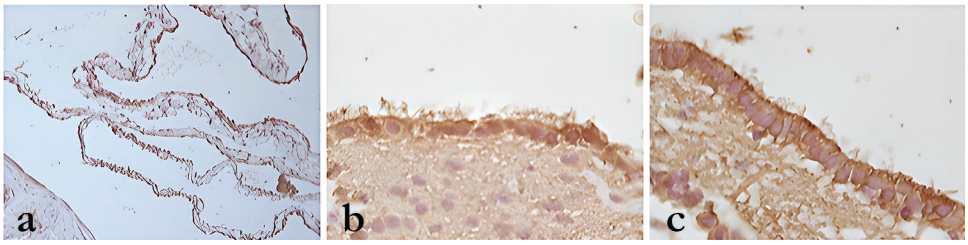


Figure 6 The cyst wall is composed of a single thin layer of cuboidal or flattened ependyma-like cells with apical cilia.



Figures 7. Photomicrograph of the cyst: cyst wall, detached from the brain **(A)**, appears as a single layer of flattened cells **(B)** (hematoxilin and eosin; A: ob.20x, B: ob. 63x). The immunohistochemical stain of the lining cells of the cyst is positive for glial fibrillar acidic protein **(C)**, which is consistent with an ependymal cyst (ob. 100x oil).

DISCUSSION

We reported the clinical, diagnostic imaging and anatomo-pathological findings of a young dog with an ependymal cyst.

Several noninfectious cystic formations exist at the intracranial site including arachnoid, neuroenteric, epidermoid and ependymal cysts. Except for arachnoidal and epidermoid cysts, no concomitant inflammatory pattern is evident in both human and veterinary literature [6]. To our knowledge this is the first case report in veterinary medicine of an ependymal cyst in a dog with concurrent CSF abnormalities that could be consistent with concurrent meningitis or meningoencephalitis or due to the intracranial congenital malformation. The CSF examination showed higher than normal protein content, with positive Pandy test.

Sampling and analysis of cerebrospinal fluid is uncommon in congenital brain diseases. In the other single case report about an ependymal cyst in a dog, CSF sampling and analysis were not performed, and the dog was euthanized and subjected to histological and immunohistochemical examination that confirmed the diagnosis of the ependymal cyst without associated inflammatory findings [7].

Epidermoid cysts contain keratin flakes and few inflammatory cells; in dermoid cysts, the cyst wall is complex and contains adnexa (sweat glands, hair follicles, and sebaceous glands [1]. Keratin has been reported as an inflammation trigger, and this would explain the finding of aseptic meningitis in the case of ruptured epidermoid and dermoid cysts [10]. In contrast, it does not explain the finding of an inflammatory CSF in the case of ependymal cysts whose contents is consistent with CSF as in the dog here reported. In human medicine, a recurrent fashion of meningitis is described and associated with dermoid and epidermoid cysts due to their rupture with leakage of their contents into subarachnoid space resulting in aseptic chemical meningitis [9,10], probably related to the contact of the meninges with keratin (non-self for the immune system).

Aseptic meningitis is referred to as a noninfective inflammation of the meninges characterized by lymphocyte-predominant pleocytosis, negative cultures, and negative polymerase chain reactions (PCRs) [9].

Aseptic meningitis could be chemical in origin when related to cysts rupture or subsequent to tumor resection, as reported in human medicine [10].

The findings of the CSF analysis in our case report were compatible with inflammation, while this finding was not confirmed with the histopathological examination. Together with the immunohistochemistry, it excludes, in differential diagnosis, the other cystic forms mentioned above.

Increased protein levels may occur in several inflammatory and non -inflammatory disorders involving the central nervous system. In these conditions, proteins may pass through dysfunctional blood–brain-barriers or be directly synthesized locally due to the disease process [9].

Pleocytosis is an aspecific finding; mononuclear pleocytosis consists of an increase in the concentration of small and mature lymphocytes and/or an increase in the number of monocytoid/macrophage cells [9]. The dog described in the present report had completed the vaccine cycle and, no previously respiratory and gastrointestinal clinical signs were reported. Thereby, we retain poorly probable an infectious etiology. Additionally, ehrlichiosis, toxoplasmosis, and neosporosis tests were negative.

Lymphoid pleocytosis has also been reported in several animals with CNS lymphoma. However, we consider unlikely that the pleocytosis we found could be attributed to a neoplastic disease, because it was not marked as it is in the course of lymphoma and due to the young age of the patient and the absence of other clinical, diagnostic imaging and laboratory findings.

It should be emphasized that prior to the CT examination, the dog was being treated with corticosteroid anti-inflammatory drugs, and by the time of the histopathological examination, the dog had been given high dose of corticosteroids for 21 days. The prolonged anti-inflammatory therapy clearly explains the lack of inflammation on histopathological examination.

Despite the considerable size of the ependymal cyst we described and the impressive mass effect on the cerebellum and brain stem, our dog was clinically normal until he was 5 months old. It was a working dog with his training already started. The evaluation of CT and MRI images did not show abnormalities resulting from sudden changes in cyst volume (e.g. perilesional edema). The characteristics of the images obtained with both advanced imaging modalities (i.e. CT and MRI), two weeks apart, suggested that the brain and cerebellar parenchyma had slowly adapted to the presence of the cyst and that this lesion had no sudden changes in size. Referring to the severe consequences on the cerebellar parenchyma and brainstem due to the mass effect and compression, it is not easy to explain how this lesion remained clinically silent for so long without giving any clinical signs.

Therefore, we can speculate that the acute symptomatology presented at about 5 months of age could be related either to reaching a threshold cyst size value beyond which the brain parenchyma could not adapt or to a concurrent inflammatory disease linked to the repetitive increase in intracranial pressure. The dog's regular sporting training could have accelerated and exacerbated the effects on intracranial pressure. Another speculation is the possible role of sporting activity in the onset of clinical signs. In fact, in human medicine, the role of sport in people with congenital intracranial diseases such as arachnoid cysts and Chiari-like malformation is controversial and could be related to an increased risk of catastrophic injuries with sudden worsening of clinical signs [11,12].

To our knowledge, there are no other case reports in literature about ependymal cysts in which concurrent CSF analysis had been done and had yielded a mononuclear pleocytosis [7].

Authors' contributions

MR, MV and SC reviewed the literature, studied the images and processed the text, ADB, FDS and RT acquired the CT images, LDS and CC took care of the anatomopathological, histological and immunhistochemical studies, AC acquired the RM study. All the authors reviewed the text and participated in the correction.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Statement of Informed Consent

The owner understood procedure and agrees that results related to investigation or treatment of their companion animals, could be published in Scientific Journal Acta Veterinaria-Beograd.

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EPENDIMALNA CISTA U KAUDALNOJ KRANIJALNOJ FOSSI MLADOG BELGIJSKOG OVČARA - MALINOA SA ABNORMALNIM NALAZOM CEREBROSPINALNE TEČNOSTI

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Šupljine u mozgu ispunjene tečnošću su dobro poznate u humanoj i veterinarskoj medicini. Urođene ili stečene cistične lezije mozga mogu biti izolovane ili povezane sa drugim bolestima. Klinički znaci koji se odnose na ciste zavise od njihove veličine i efekta mase na okolne neuroanatomske strukture. Predstavljamo slučaj petomesečnog belgijskog ovčarskog psa - Malinoa sa bolom u vratu i nagnutom glavom udesno. Pas je imao normalan hematohemijski profil i negativne testove na zarazne bolesti. Skeniranje kompjuterizovanom tomografijom sa poboljšanjem kontrasta otkrilo je prisustvo cistične lezije tankih zidova u kaudalnoj lobanjskoj jami na nivou desnog pons-cerebelarnog spoja. Pukcijom likvora lumbalnom punkcijom je otkrivena monocitna pleocitoza. Nakon početnog poboljšanja nakon terapije kortikosteroidima i antibioticima, klinički znaci su se pogoršali, a pas je podvrgnut drugoj kliničkoj evaluaciji i pregledu magnetnom rezonancom. Nakon eutanazije obavljen je kompletan obdukcioni pregled. Histološki i imunohistohemijski nalazi su ukazivali na ependimalnu cistu.