Intracranial Cholesterol Granuloma in a Cat

Emanuele RICCI1*, Gianluca ABBIATI2 and Carlo CANTILE1

1)Department of Animal Pathology, Faculty of Veterinary Medicine, University of Pisa and 2)Veterinary Clinic “Malpensa”, Samarate (Varese), Italy

ABSTRACT. A case of intracranial cholesterol granuloma is described in a 4-year-old neutered European male cat presented with a 5-month history of progressive weakness, ataxia and depression. On clinical evaluation, haematological and biochemical profiles revealed only mild hypercholesterolemia and magnetic resonance imaging showed a large space-occupying extra-axial mass in the area of the falx, not homogeneous after contrast enhancement. At post-mortem examination, an orange-yellowish mass of 22 mm in diameter extended from the right frontal lobe to the temporo-parietal region, causing atrophy of the prosencephalic region of the brain. The site of origin of the mass was within the subarachnoid space of the supracallosal sulcus of the right cerebral hemisphere. Histological examination of the lesion revealed abundant deposits of cholesterol clefts, surrounded by clusters of macrophages and multinucleated giant cells. Neither inflammatory lesions, nor cholesterol deposits were detected in other areas of the brain and in other organs. On the basis of the histological examination, a diagnosis of intracranial cholesterol granuloma was made.

KEY WORDS: cholesterol granuloma, feline, MRI, nervous system disease.

Cholesterol granulomas (CGs) are known as well circumscribed, non neoplastic lesions, resulting from a chronic inflammatory reaction to continuous deposition of cholesterol crystals [10]. In human beings, a diagnosis of CG has been established in several sites throughout the body, comprising the intracranial localisation [4, 13, 20].

In veterinary medicine, the development of an intracranial cholesterol granuloma has been described as an incidental, asymptomatic finding at necropsy in 20% of older horses and the choroid plexus of fourth and lateral ventricles represented the preferential location of the so-called “cholesteatoma of the choroid plexus” [9]. Sporadic descriptions of identical intracranial lesions have been reported in other animals, such as meerkats (Suricata suricatta sp., family Herpestidae) [2, 21, 22], lemurs [11], reptiles [19], Cuban tree frogs [16] and leaf-tailed geckos [5]. Single cases have been described in one bear [27], one dog [23] and one cat [3].

A 4-year-old neutered male cat was presented at the “Malpensa” Veterinary Clinic (Samarate, Italy) with a 5-month history of progressive weakness, ataxia and depression. The cat was previously treated with prednisone with partial remission of clinical signs. On clinical examination, the cat appeared dehydrated and in poor general condition. At presentation the cat exhibited aggressive behaviour and only a limited number of neurological tests could be performed. Neurological examination revealed proprioceptive deficits in all four limbs, no evident abnormality of cranial nerves and a poor bilateral menace reaction. On the basis of the clinical data, a forebrain lesion was suspected. Differential diagnoses included encephalitis, neoplasia, toxic, metabolic or nutritional encephalopathy. Haematological and biochemical profiles revealed moderate hyperglycaemia (343 mg/dl, normal range: 60–175 mg/dl) and mild hypercholesterolemia (236 mg/dl, normal range: 97–207 mg/dl). A cerebrospinal fluid (CSF) sample was obtained with a lumbar tap and PCR analyses for toxoplasmosis and feline infectious peritonitis were performed. Biochemical and cytological analysis of the CSF revealed normal cell count and protein content, and PCR analysis yielded negative results. Magnetic resonance imaging (MRI) was performed with a 0.22 Tesla unit (Paramed-MrJ). Sequences included a Fast Spin Echo (FSE) T2, a Fluid Attenuated Inversion Recovery (FLAIR) and Spin Echo (SE) T1 repeated after gadolinium injection (Gd-DTPA, 0.1 mmol/kg). The neuroradiographic study showed the presence of an extra-axial large space-occupying lesion in the area of the falx. The mass appeared round-shaped, more expanded to the right side and extending from the frontal to the occipital lobes. The margins appeared sharp and irregular. Mass effect was pronounced and compression of the brain stem structures and cerebellar herniation were observed. The mass appeared isointense in FSE T2 and FLAIR sequences, and not homogeneously hypo-isointense in T1 with an inner part hyperintense in T2. In all sequences, fine granulations hyperintense in T2 and slightly hypointense in T1 were seen. A moderate and irregular enhancement appeared after gadolinium injection, especially along the margins and in the central area of the mass. The previously described central area was markedly enhanced. MRI also showed a large hydroxyringomycotic cavity of the cervical spinal cord (Figs. 1A, 1B and 1C). On the basis of the clinical and neuroradiographic findings, a meningioma or a cholesterol granuloma was suspected. Because of the poor condition of the cat and the poor prognosis the cat was euthanatized upon owner’s request.

At post-mortem examination, gross abnormalities were
limited to the brain and cervical spinal cord. A medial mass extended from the frontal to the temporo-parietal lobe of the right hemisphere. In serial transverse sections of fixed brain, the mass was well circumscribed, orange to yellow, with a maximum diameter of 22 mm, and severely displaced and compressed both the cerebral hemispheres, thalamus and midbrain (Fig. 1D). The mass did not involve the lateral ventricles and did not originate from the choroid plexus. The site of origin of the lesion was within the subarachnoid space of the supracallosal sulcus of the right cerebral hemisphere. Transverse and longitudinal sections of the spinal cord confirmed the presence of a hydrosyringomyelic cavity, interpreted as the result of a hydrodynamic compensation due to increased intraventricular pressure. The nervous tissue and representative samples of major organs were fixed in phosphate-buffered 4% formalin solution and routinely processed for histology. Selected sections of paraffin-embedded tissue were stained with haematoxylin and eosin, periodic acid-Schiff (PAS), Luxol fast blue and Goldner trichrome methods. Sections also were examined for immunohistochemical reactivity to a macrophage marker (mouse monoclonal antibody, clone HAM-56, Cell-Marque Corp., U.S.A.). A polymer-based system was used as secondary antibody (EnVision system-HRP, DakoCytomation, Carpinteria, U.S.A.). Samples of the mass were also frozen in isopentane precooled in liquid nitrogen and cryostatic sections were stained with Shultz method for cholesterol and with Oil red O for neutral lipids [15].

Histologically, the lesion had the characteristics of a chronic granuloma. The mass was mainly composed of aggregates of macrophages and foreign-body giant cells surrounding cholesterol crystals (Figs. 2A and 2B). The macrophage marker HAM-56 was strongly expressed by many cells (Fig. 2C). At the periphery of the mass, scattered clusters of lymphocytes and proliferation of capillaries were sometimes observed, along with several erythrocytes and haemosiderin-laden macrophages. The granuloma was well demarcated by a continuous leptomeningeal layer. The surrounding neuroparenchyma was severely atrophic with loss of neurons, extensive gliosis and degeneration of the white matter. In paraffin-embedded tissue sections, the cholesterol crystals appeared as empty clefts, whereas ORO and Shultz methods allowed to detect the presence of small intracytoplasmic droplets of neutral lipids within macrophages and green cholesterol crystals (Fig. 2D), respectively. On the basis of its morphological and histochemical features, the lesion was consistent with a cholesterol granuloma. No cholesterol deposits were observed within the
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...as well as in other areas of the brain and other organs. Deposition of cholesterol crystals is a feature frequently observed in feline meningiomas [24]. Particularly, the “granular-cell” subtype, whose meningeal origin is however on debate, shows remarkable deposits of cholesterol crystals in a sheet of pleomorphic, sometimes multinucleated, round PAS-positive granular cells [12]. In our case, the lesion was exclusively constituted by lipid-laden, PAS-negative, HAM-56-positive macrophages with many old and recent multifocal haemorrhages. Moreover, neither mitotic figures, foci of calcification, nor psammoma bodies were observed.

Intracranial CGs have been described in dogs [23] and in captive meerkats as large granular masses covering the meninges of the dorsal aspect of the encephalon [2, 21, 22]. In the feline species, reports of extracranial CGs have been described [7, 8, 28], but only one description of an intracranial CG has been recorded in an old cat [3]. The lesion developed in the longitudinal cerebral fissure and showed histopathological features very similar to the case of our report. In that cat, serum cholesterol concentration was at the upper limit of the normal range.

Pathogenesis of CG is still unclear. Since the cholesterol is a normal constituent of mammalian cell membrane and it accounts for approximately 25% of total lipid content in the membrane of erythrocytes [14], it has been hypothesized that chronic and intermittent bleedings could play a key role in promoting the cholesterol deposition [26]. Putative causes on the basis of the haemorrhages might include congestion of the mucosal surface with secondary extravasations of erythrocytes [6] or chronic and repeated inflammatory events resulting in scattered haemorrhages [28]. Indeed, in CG many erythrocytes are usually intermingled with the empty clefts and the higher proportion of cholesterol concentration, instead of its esters, demonstrates that the lipid is derived from erythrocytes rather than from serum [17, 18]. Impaired ventilation of aerated bones, the lack of an effective lymphatic drainage, and traumatic events are mentioned as concurrent causes for intramucosal congestion and haemorrhages in human CG pathogenesis [20]. In our cat, the observation of haemosiderin-laden macrophages at the periphery of the cholesterol granuloma could be indicative of previous subarachnoid local haemorrhage, whose cause remains undetermined.

High levels of cholesterol serum concentration might be involved in the development of CG. Francis et al. [4] described an intracerebral cholesterol granuloma in a case of human familial hypercholesterolemia, and Kotevoglu and Yesilten [10] described the spreading of subcutaneous cholesterol-containing nodules in a dysbetalipoproteinemic patient. Experimentally, a hyperlipidic diet was successfully used to produce xanthomas of the choroid plexus in rabbits [1]. Two lemurs (fat-tailed dwarf, Cheirogaleus...
medius spp.) developed a cerebral CG as a consequence of a hyperlipidemic condition [11]. The development of CG in hypercholesterolemic conditions has also been suggested by other studies [2, 6, 22].

Accurate descriptions of MRI characteristics of feline intracranial masses exist in literature [25]. By the evaluation of our MRI results, since an ovoid, encapsulated and extra-axial mass was observed, the list of differential diagnoses was restricted to meningioma and CG. The finding of a heterogeneous contrast uptake can be suggestive of CG with scattered areas of haemorrhage [3].

In conclusion, CG should be added to the list of the differential diagnoses in cats with intracranial space-occupying lesions, even in absence of significant dyslipidemic findings.

REFERENCES