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CASE REPORT

Companion or pet animals

Clinical, imaging and histopathological features of concurrent malignancies in a dog: Meningoencephalitis of unknown origin and a malignant parotid gland carcinoma

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Abstract

Parotid gland tumours are rare in dogs. In this report, a 7-year-old, female, spayed bearded collie was presented for a subacute onset of neurological signs. A meningoencephalitis of unknown origin affecting the cerebellum diagnosed 10 months before had successfully been treated with prednisolone and mycophenolate mofetil. Head CT and MRI showed a right-sided retropharyngeal mass invading the caudal fossa and compressing the cerebellum and brainstem, adjacent to a second lesion involving the right parotid gland. Postmortem examination revealed a malignant parotid gland carcinoma with intracranial extension, occipital bone infiltration and metastasis to the lungs and the right medial retropharyngeal lymph node. The cerebellum was unremarkable. This is the first report describing detailed imaging features of a malignant parotid gland carcinoma developed in a dog previously diagnosed with a meningoencephalitis of unknown origin.

BACKGROUND

Salivary gland tumours are rare neoplastic disorders in dogs with an overall incidence of 0.17%.[1] They are usually firm, painless masses attached to the deeper structures in the neck[2] and often have an invasive growth pattern, so they can infiltrate adjacent tissues.[3] Metastases to the regional lymph nodes and other organs, such as lungs and bones, have also been described.[4] So far, most reports focus on histopathological aspects of the tumour,[2,5,6] but salivary gland carcinomas invading the skull have not yet been described. The aim of this case report was to describe a dog treated with an immunomodulatory protocol for a suspected meningoencephalitis of unknown origin, presented for a malignant salivary gland carcinoma 10 months after treatment start.

CASE PRESENTATION

A 7-year-old, female, neutered bearded collie was presented with a 1-week history of progressive gait abnormalities. An initial treatment with meloxicam (Metacox; Graeub) and amoxicillin-clavulanic acid (Clavubactin; Graeub) prescribed by the referring veterinarian had not improved the clinical signs.

Abnormal findings in the physical examination included obtunded consciousness and reddish, dry mucous membranes compatible with compensated shock. Abnormal findings in the neurological examination were lateral recumbency, opisthotonus, head tilt and head turn to the left side. Ambulation was severely impaired due to a vestibular ataxia, which also compromised the correct evaluation of the postural reactions. The examination of the cranial nerves revealed a jerk rotatory nystagmus with the fast phase to the right side. When testing the spinal reflexes, an increased muscle tone on the right side was noticeable, but otherwise spinal reflexes were unremarkable. No spinal pain could be elicited by palpation of the back and neck. The findings of the neurological examination were consistent with a central vestibular system lesion.

Given the history and neurological findings, the following differential diagnoses were considered: inflammatory (infectious vs. non-infectious meningoencephalitis), neoplastic (primary or secondary brain tumour), degenerative (storage disease) or, less likely, vascular (haemorrhage) diseases.

Haematology, serum biochemistry and coagulation profiles were performed. The results showed a minimal increase of prothrombin time (PTT) (17.8 seconds, reference interval 9.6–16.1 seconds), a moderate increase of fibrinogen (486 mg/dl, reference interval 150–300 mg/dl) and a mild increase of

LEARNING POINTS/TAKE HOME MESSAGES

- A mass lesion in the neck—more specifically a parotid gland carcinoma—can lead to both peripheral and central vestibular clinical signs via formation of metastasis and invasion of the skull through the jugular foramen.
- Magnetic resonance imaging characteristics of salivary gland carcinomas include T1- and T2-weighted hyperintensity as well as marked heterogeneous contrast enhancement.

canine C-reactive protein (CRP) (16.6 mg/L, reference interval <10.7 mg/L).

For further assessment of a possible lesion causing the clinical signs, the dog underwent MRI examination of the brain using a 1.0-Tesla open permanent magnet (Philips Panorama HFO, Philips Medical Systems, PC Best, Netherlands). Sequences acquired included transverse T2-weighted (T2w), sagittal T2w, transverse T2w-fluid-attenuated inversion recovery (FLAIR), dorsal T2w-FLAIR, transverse T1-weighted (T1w), transverse T2*, ADC, DWI, dorsal T1w 3D, as well as dorsal T1w 3D and transverse T1w after contrast administration of 0.15 mmol/kg acidum gadotericum (Omniscan 0.5 mmol/ml). The following findings were observed (Figure 1a–d). There were bilateral asymmetrical lesions in the grey and white matter of both cerebellar hemispheres and the cerebellar vermis. These lesions were ill-defined, hyperintense on the fluid-sensitive sequences (T2w, T2w-FLAIR, T2*) and hypointense on T1w sequences with marked contrast enhancement mainly in the periphery. Additionally, a generalised cerebellar swelling with moderate compression of the brainstem, caudal herniation into the foramen magnum and dilation of the third ventricle were visible. There was a moderate right-sided retropharyngeal lymphadenomegaly. The remaining soft tissues, including the salivary glands, were within normal limits. A T2w hyperintense focus was visible on the T2w sagittal sequence (Figure 1d) at the level of the interthalamic adhesion, consistent with partial volume artefact from hyperintense cerebrospinal fluid (CSF) in the peripheral CSF spaces. After MRI examination, the list of differential diagnoses was narrowed to infectious meningoencephalitis (*Neospora caninum*, canine distemper virus) versus meningoencephalitis of unknown origin (MUO).

The following additional examinations were conducted to reach a final diagnosis. CSF was obtained by cisternal puncture; the analysis indicated a moderate elevated protein level and moderate mixed pleocytosis, with a total nucleated cell count (TNCC) of 165 cells/μl containing 53% neutrophils and 40% lymphocytes (normal TNCC <5 cells/μl). A microbiological culture as well as PCR of miscellaneous infectious diseases of the CSF (*Bartonella* species, *Borrelia* species, canine distemper virus, *Neospora caninum*, *Toxoplasma gondii*, *Cryptococcus neoformans*) were all negative. Thus, an MUO was considered the most likely differential diagnosis in this case.

The medical treatment initiated while waiting for the PCR results included one intravenous injection of dexamethasone (Dexadreson; MSD) (1 mg/kg), followed by oral prednisolone (Prednisolon; Streuli Pharma) (0.5 mg/kg once daily) as well as intravenous clindamycin (Clindamycin Phosphat; Pfizer) (10 mg/kg twice daily) and oral trimethoprim/sulfamethoxazolum (Bactrim forte; Roche Pharma) (15 mg/kg twice daily). After excluding infectious diseases, antimicrobial therapy was discontinued and an immunomodulatory treatment protocol consisting of oral prednisolone 1 mg/kg once daily was started. At the first clinical and neurological follow-up 28 days later, the dog showed clear improvement of the previous observed neurological deficits. Unfortunately, severe side effects (severe polyuria/polydipsia [PU/PD], muscle atrophy, hair loss, thin and scaly skin), likely caused by the corticosteroid treatment, were reported. Consequently, the treatment protocol was adjusted and oral mycophenolate mofetil (Mycophenolat mofetil; Sandoz) (12.5 mg/kg twice daily) was added in order to reduce the prednisolone dosage gradually. Hereafter, the dog showed a rapid improvement of its general status as well as resolution of the previously described side effects. The neurological examination 8 weeks after diagnosis was unremarkable.

A follow-up MRI (same protocol as during the first scan with additional assessment of T2 drive and transverse 3D WATS) 3 months after diagnosis showed a complete regression of the previously reported cerebellar lesions and a mild atrophy of the cerebellum and cerebrum (Figure 1e). Retropharyngeal lymph nodes were within normal limits. Cisternal CSF analysis was unremarkable.

As the clinical, imaging and laboratory findings indicated a remission of the previously diagnosed MUO, the dosages of both prednisolone and mycophenolate mofetil were gradually reduced.

The dog was still neurologically normal 10 months after the initial presentation, receiving mycophenolate mofetil 12.5 mg/kg every other day, while prednisolone was successfully discontinued 6 weeks previously. However, by that time the owners reported mild upper airway signs (dysphonia), for which the dog was treated with bromhexin (Bisolvon; Sanofi-Aventis) and meloxicam by the referring veterinarian.

Three days after discontinuation of mycophenolate mofetil, the dog started showing respiratory difficulties with coughing and hypersalivation, and it was presented again at our hospital. Upon general physical examination, the dog was tachypnoeic with a respiratory rate of 60 breaths per minute and had increased inspiratory noises of the upper airways (stridor). A large (6–7 cm), firm mass could be detected by palpation at the base of the right ear. The anatomical origin of the mass could not clearly be identified, although a connection with the thyroid gland or one of the regional lymph nodes was suspected. Abnormalities during neurological examination included difficulties to locate noises, mild head tilt to the right side and a mild vestibular ataxia (drifting to the right). Testing the postural reactions revealed a mildly reduced proprioceptive positioning on the left side, but was otherwise normal. The examination of the cranial nerves revealed a right-sided miosis, enophthalmus, protrusion of the third eyelid (Horner's syndrome) and ventral positional strabismus. In addition, the dog exhibited a positional horizontal/rotatory nystagmus with the fast phase to the left side, and consequentially the gag reflex could not be elicited. These findings were compatible with a right-sided extra-axial lesion involving multiple cranial nerves (CN VIII, IX, X + sympathetic innervation of the eyes) or a lesion of the caudal brainstem. Haematology and serum

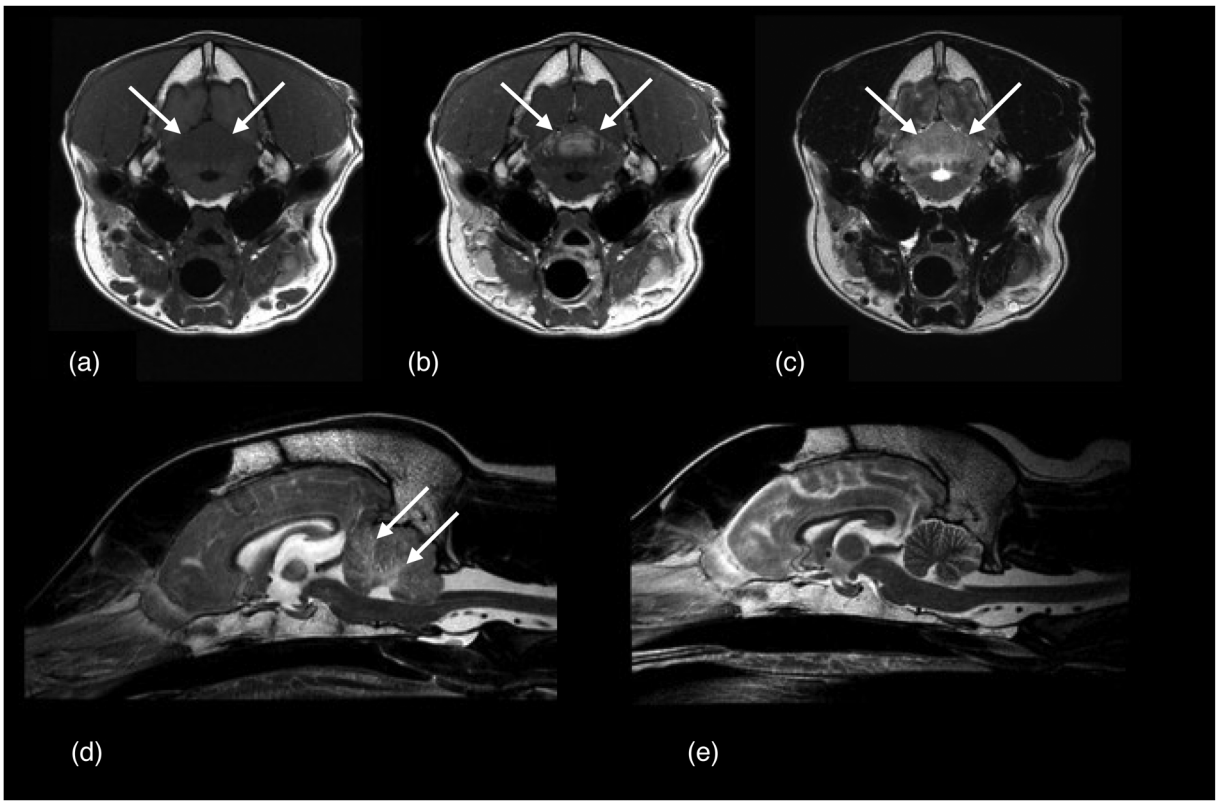

FIGURE 1 MRI of the brain at initial presentation (a–d) and at the three-month follow-up (e). (a) T1w transverse image precontrast at the level of the cerebellum; (b) T1w transverse image postcontrast at the level of the cerebellum; (c) T2w transverse image at the level of the cerebellum; (d) T2w sagittal image; (e) T2w sagittal image. There are several asymmetrical lesions in the grey and white matter of the cerebellar hemispheres and cerebellar vermis (arrows). The lesions are hyperintense on T2w images (c and d) and hypointense on T1w images (a) showing marked contrast enhancement (b). There is a generalised cerebellar swelling with moderate compression of the brainstem and caudal herniation into the foramen magnum (d). Moderate dilation of the third and fourth ventricles is visible (c and d). T2w hyperintense focus (d) at the level of the interthalamic adhesion is consistent with partial volume artefact. The MRI performed 3 months after diagnosis showed a complete resolution of the previously reported cerebellar lesions and no dilation of the ventricles. There is no caudal herniation of the cerebellum into the foramen magnum, but there is mild atrophy of the cerebellum and cerebrum (e)

biochemistry revealed no major abnormalities apart from a moderate increase of canine CRP (57.1 mg/L, reference interval <10.7 mg/L).

INVESTIGATIONS

At this time point, the main differential diagnosis was a malignant process; therefore, a whole-body CT (CT Brilliance 16, Philips) as well as an MRI examination of the brain were performed (Figure 2a–f). The CT showed a large heterogeneous and heterogeneously contrast-enhancing mass in the right retropharyngeal space (measuring 4, 3.5 and 9 cm in width, height and length, respectively). There was osteolysis of the right occipital bone and of the axial and dorsal parts of the temporal bone. The mass was extending into the caudal cranial fossa through the enlarged right jugular foramen and invading the dorsal aspect of the right tympanic bulla. Additionally, a second smaller lesion with similar tomographic characteristics was visible lateral to the first mass in the region of the right parotid salivary gland. There was no defined separation between the two lesions on all planes, as they were adjacent; however, they appeared separated rostrally and caudally and appeared to be compatible with a retropharyngeal mass (larger lesion, described as first one) and the abnormal parotid salivary gland. The CT also showed a few pulmonary nodules measuring up to 13 mm in diameter. They showed soft tissue attenuating values and moderate relatively homogeneous contrast enhancement. Sequences acquired for MRI included transverse T2w, sagittal T2w, transverse T2w-FLAIR, dorsal T2w-FLAIR, transverse T1w, transverse T2*, dorsal T1w 3D, as well as dorsal T1w 3D and transverse T1w after contrast administration of 0.15 mmol/kg acidum gadotericum (Omniscan 0.5 mmol/ml), and transverse 3D WATS. In MRI, the described retropharyngeal mass lesion was T2w and T1w hyperintense to the muscles and showed marked heterogeneous contrast enhancement. It caused compression of the myelencephalon and the right cerebellar hemisphere shifting them to the left side. The second smaller lesion visible at the level of the right parotid salivary gland was also visible, showing heterogeneous intensity, being T2w and T1w hyperintense to the muscles and showing marked heterogeneous contrast enhancement. CSF obtained by cisternal puncture was unremarkable.

DIFFERENTIAL DIAGNOSIS

CT and MRI findings were compatible with an aggressive neoplastic process involving the right medial retropharyngeal lymph node with extension into the cranium. Involvement of the right parotid salivary gland was additionally suspected

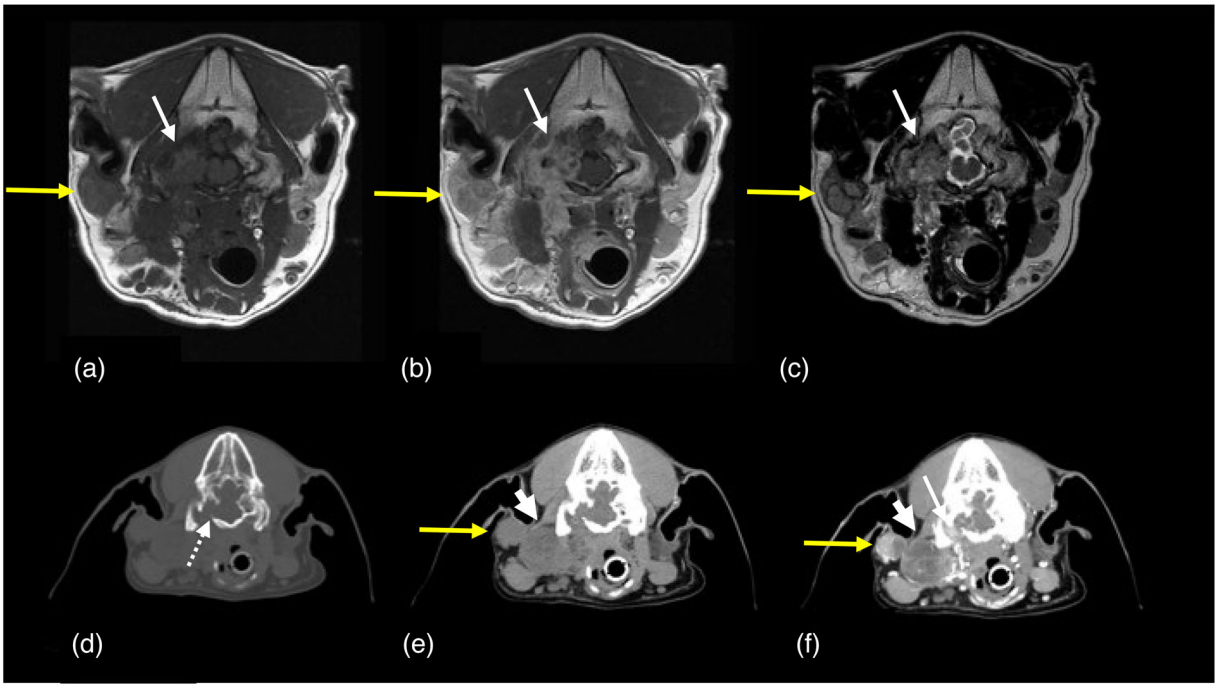

FIGURE 2 MRI (a–c) and CT (d–f) images obtained 10 months after the initial diagnosis of meningoencephalitis of unknown origin (MUO). All the images are at the level of the cerebellum. (a) T1w transverse image precontrast; (b) T1w transverse image postcontrast; (c) T2w transverse image; (d) CT transverse image reconstructed with the bone filter; (e) CT transverse image reconstructed with the soft tissue filter precontrast; (f) CT transverse image reconstructed with the soft tissue filter postcontrast. There is a large T1w and T2w heterogeneous and heterogeneously contrast enhancing mass in the right retropharyngeal space (e and f; short arrow). This lesion is extending caudally and dorsally into the caudal cranial fossa (a–c and f; long arrow) through the enlarged right jugular foramen (d; dashed arrow) and causing compression of the right cerebellar hemisphere. This lesion is heterogeneous and showing marked and heterogeneous contrast enhancement also on CT images (f). There is a second, smaller lesion with similar tomographic characteristics lateral to the first mass in the region of the right parotid salivary gland (a–c, e and f; yellow arrow)

with similar characteristics and no definitive visible separation from the retropharyngeal mass.

OUTCOME AND FOLLOW-UP

The dog was euthanized at the owner's request because of the strong suspicion of a malignant metastatic process of the parotid gland with intracranial extension, involvement of the adjacent bones as well as subsequent metastasis into the right medial retropharyngeal lymph node and the lungs. A postmortem examination was performed and revealed that the large mass lesion in the right retropharyngeal space diagnosed in CT consisted of a malignant salivary gland carcinoma of the right parotid gland (Figures 3a–c and 4). The salivary gland carcinoma itself extended intracranially and infiltrated the occipital as well as the temporal bone and metastasised to the lungs and the right medial retropharyngeal lymph node (Figure 5). The brainstem showed mild acute haemorrhages, which might have been due to vascular damage following compression by the neoplasia. The cerebellum showed no major abnormalities on histopathology; therefore, the treatment of the MUO was considered as successful.

DISCUSSION

Salivary gland tumours are rare neoplastic disorders in dogs with an overall incidence of 0.17%.[1] They are usually firm, painless and attached to deeper structures in the neck.[2] They often have an invasive pattern of growth, so they can extend through the capsule of the gland to infiltrate adjacent tissues.[3] Furthermore, metastasis in regional lymph nodes and other organs, such as lungs and bones, are also described.[7] There can be nodal involvement in 17% and distant metastases in 8% of cases at the time of diagnosis.[8] One case report described a parotid salivary gland adenocarcinoma with bilateral ocular and osseous metastases in a dog[4]; another one reported a carcinosarcoma of the mandibular salivary gland extending into the adjacent muscular tissues and the jugular vein.[9] Neither of these reports included imaging characteristics of the described mass lesions.

In this report, we describe an acute onset of clinical signs due to a parotid gland carcinoma after complete withdrawal of immunomodulatory medication for a previously diagnosed MUO. So far, the pathogenesis of MUO is still not completely understood, although an autoimmune pathogenesis involving both genetic and environmental factors is suspected.[10–12] The absence of a standard specific treatment protocol reflects the gaps in understanding the disease complex. Currently, common immunomodulatory drugs used in MUO patients include prednisolone and/or cyclosporine, mycophenolate mofetil, or cytosine arabinoside.[13–16] Depending on the subtype of the disease and specific features, the prognosis is fair to poor.[17] Not many studies evaluated the outcome of dogs affected by MUO, and the majority of dogs affected by the necrotizing forms die or are euthanized due to progression or severe clinical signs within weeks to months.[18] According to Lowrie et al.,[19] repeated MRI and CSF analysis during treatment for MUO appears a useful prognostic tool, with resolution of lesions at 3 months suggesting a good or excellent long-term outcome. Following the recommendations of the latter study in the presented dog, MRI and CSF

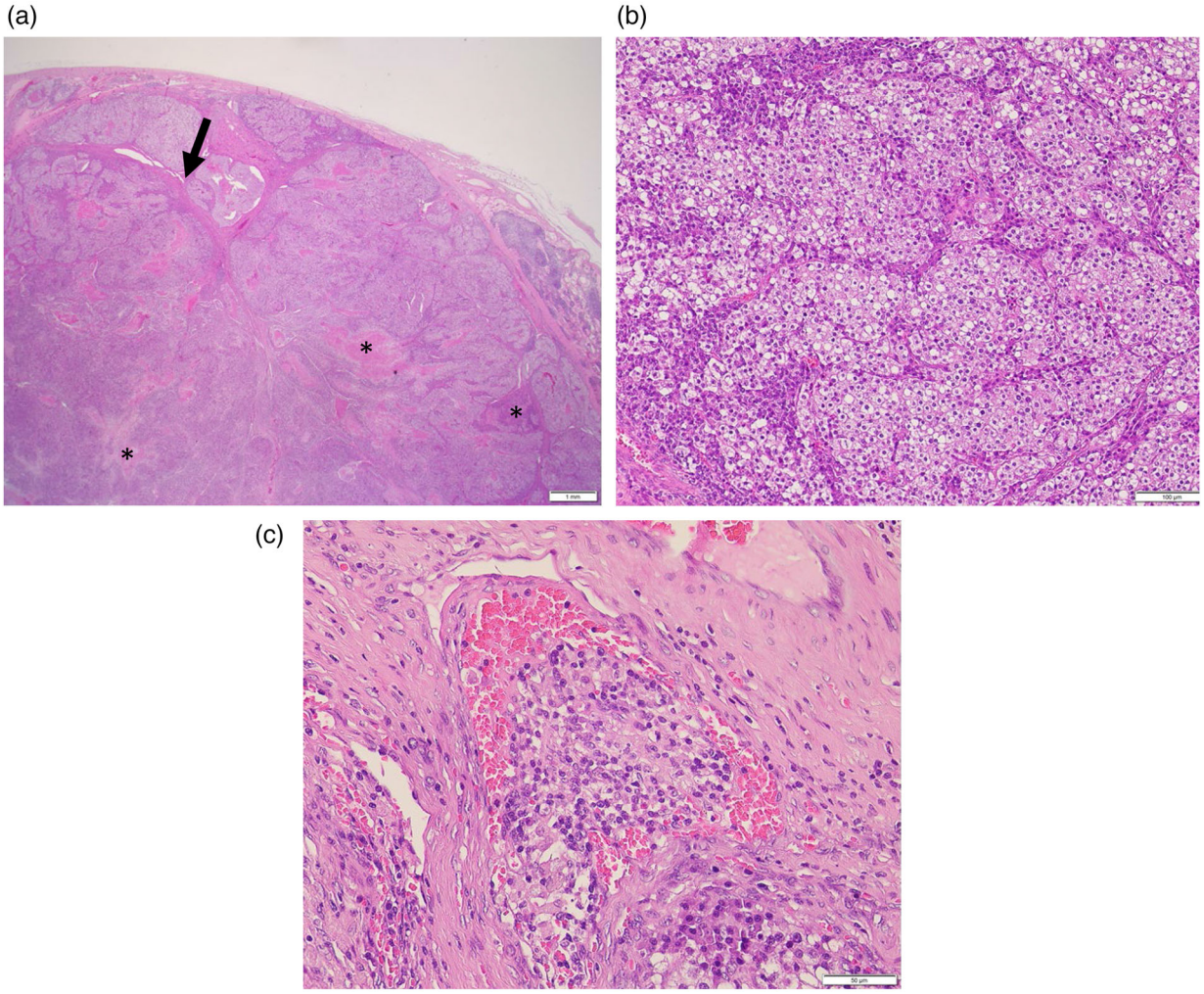

FIGURE 3 Microphotograph of the salivary gland carcinoma of a 7-year-old, female, spayed bearded collie. The mass consisted of multiple neoplastic nodules separated by variably sized septae of dense connective tissue (arrow) with multifocal to coalescing areas of necrosis (asterisk) (a). Higher magnification view of the cellular architecture and morphology of the mass (b). Higher magnification view of the vascular invasion by neoplastic cells (c). Haematoxylin and eosin stain

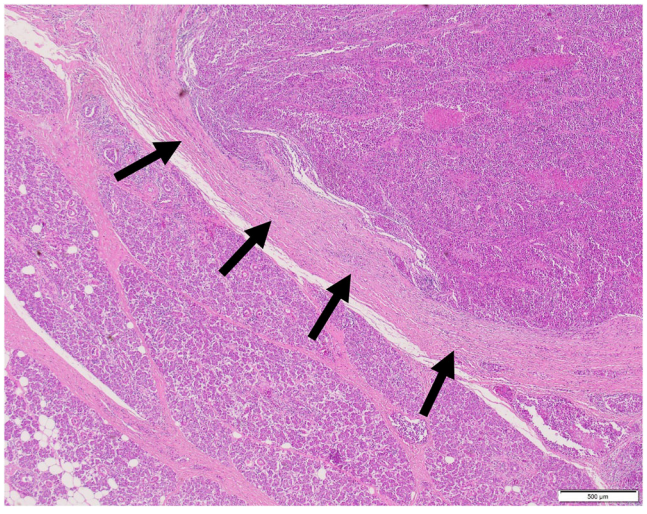

FIGURE 4 Section of the glandula parotis encapsulated mass (arrows) next to healthy glandular tissue

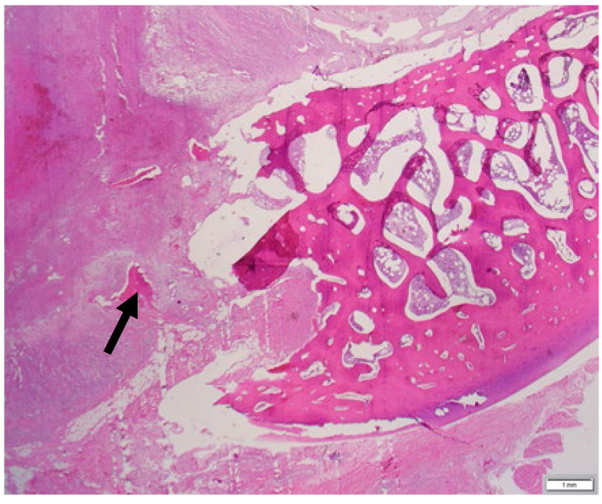

FIGURE 5 Section of the os temporale with focal extensive replacement and infiltration by the neoplastic cells. In between the neoplastic cells, remaining trabecular bone was present (arrow)

examinations were repeated 3 months after starting the therapy. Previously visible MRI lesions resolved and CSF examination was unremarkable; therefore, it was decided to wean off the treatment over several months. The clinical and imaging remission was confirmed 10 months after initial diagnosis of MUO via histopathological examination of the cerebellar tissue, which did not show any abnormalities. Thereby, the success of the used immunomodulatory treatment protocol in this case could be confirmed.

Even though treatment for the suspected MUO was successful, the dog started having other clinical signs at the time of complete withdrawal of the immunomodulatory therapy, and postmortem was diagnosed with a malignant parotid gland carcinoma.

Treatment options in canine salivary gland carcinomas include surgical removal, radiotherapy and chemotherapy.[3] In this case, surgical removal was not an option at the time of presentation due to the extensiveness of the tumour with involvement of intracranial structures. Little information about radiotherapy or chemotherapy in similar cases is available. In human medicine, the standard of care involves surgery to remove the primary tumour followed by adjuvant radiotherapy in those high-risk tumours[20,21]; a similar approach has been used in dogs with malignant salivary gland tumours.[22] Combined surgery and radiotherapy in humans has been shown to be superior to radiotherapy alone.[20] As salivary gland carcinomas may be associated to local recurrence and distant metastasis, adjuvant chemotherapy is often considered.[23] However, the use of chemotherapy for salivary gland tumours has not yet been explored in dogs.[6]

In the present case, the carcinoma became clinically evident at the very same time the dog was weaned off the immunomodulatory treatment, received for the previously diagnosed MUO.

In humans, studies regarding a connection between immunosuppression and the development of malignant lesions have especially been performed in patients undergoing organ transplantation and therefore receiving long-term immunosuppression, using different immunosuppressive agents. Summarising previous studies, Engels et al.[24] demonstrated a two- to four-fold elevated risk for malignancies in these patients.[24]

A few studies that investigated an increased risk of developing malignancy using a chronic treatment with mycophenolate mofetil are available and show contradictory results: one described an increased risk for the development of a malignant lesion using mycophenolate mofetil compared to everolimus.[25] In contrast, another study states that patients receiving mycophenolate mofetil had a significantly lower risk of developing malignancy.[25–27] No such studies have been done to investigate related adverse effects caused by either prednisolone or mycophenolate mofetil in dogs. Considering what has been reported in the literature, it is unclear if the development of a neoplasm in this dog could be related to the previous immunomodulatory treatment. The chronic immunomodulatory treatment might have been carcinogenic itself, might have prevented an adequate reaction of the immune system to the development of a neoplastic mass lesion, or the immunomodulation might even have slowed down the growth of a previously present neoplastic mass.

Ultimately, it should be considered that individuals affected by a tumour type are prone to develop other neoplastic lesions; current studies in human medicine even found an increased incidence of multiple concurrent malignancies.[28] Unfortunately, in the present case, it is unclear if both diseases were comorbidities and the MUO was cured, if the changes in the cerebellum presented a neoplastic instead of an inflammatory lesion or if the MUO and/or the immunomodulatory treatment played a role in the development of the neoplastic lesion. Moreover, there was no histopathological confirmation of the MUO during the acute presentation, but the diagnosis was based on clinical parameters as recommended by Granger et al.[29] At the time of the initial diagnosis of MUO, a right-sided retropharyngeal lymphadenopathy was present, but no further investigations were performed (e.g., fine-needle aspiration). The lymphadenopathy resolved in the later clinical as well as MRI follow-up examinations. Although a reactive lymphadenopathy was suspected at that time, an early malignant infiltration of the lymph node, possibly suppressed by the following immunomodulatory treatment, could not be ruled out.

CT characteristics of salivary gland neoplasia have been reported in veterinary medicine, and are consistent with a mass originating from the salivary gland and showing irregular and heterogeneous contrast enhancement, as the one described in this patient.[30] One case report described ultrasound and multidetector CT findings of mandibular salivary gland adenocarcinoma in two dogs.[31] Primary salivary gland neoplasia might be difficult to differentiate from other soft tissue masses infiltrating the salivary gland (such as fibrosarcoma). MRI is not commonly used for the diagnosis of salivary gland diseases. However, MRI characteristics of salivary gland neoplasia in general, but not specifically for parotid gland carcinomas, have been described and similarly to CT they include an irregular mass originating from the salivary gland showing mixed signal intensity on T1w and T2w images with mostly strong and heterogeneous contrast enhancement, and this positively correlates to the MRI features described in this case.[32] MRI characteristics of zygomatic gland diseases, including one case of neoplasia, have also been described[33] and are comparable to the findings of the parotid gland carcinoma described here: hyperintensity in T1w and T2w images with marked contrast enhancement.

In conclusion, the CT and MRI characteristics of salivary gland neoplasia have been described in dogs and cats[34] and were confirmed in this case. However, this is the first description of the detailed MRI characteristics of a parotid gland carcinoma in a dog. Moreover, despite the well-recognised aggressive behaviour of salivary gland carcinomas, to the authors' knowledge, this is the first report of regional lymph node metastasis and invasion of the skull through the jugular foramen, as well as extension into the caudal cranial fossa, causing compression of the myelencephalon and the cerebellum. Therefore, when a lesion similar to the one described in this case develops, a salivary gland carcinoma should be considered in the differential diagnosis in dogs presented with a cervical mass lesion and central nervous system-associated clinical signs.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

ETHICS STATEMENT

This is a report on a clinical case. All procedures were performed following client's consent.

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