Opportunistic *Candida albicans* infection with granulomatous meningoencephalitis and aggressive osteolysis

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Opportunistische *Candida-albicans*-Infektion mit granulomatöser Meningoenzephalitis und aggressiver Osteolyse

Opportunistische Candida-Infektionen des Zentralnervensystems werden zunehmend bei immungeschwächten Menschen beobachtet und wurden kürzlich bei drei Hunden beschrieben. Bei Hunden wurde jedoch die bei Menschen gelegentlich vorkommende Manifestation der Osteolyse im Schädelknochen bei einer chronischen Candida-Infektion noch nicht diagnostiziert.

Dieser Bericht beschreibt den Fall eines zehnjährigen immungeschwächten Bullterriers mit zerebralen Läsionen. Magnetresonanztomographie (MRT) und Computertomographie (CT) zeigten eine Meningoenzephalitis und multifokale aggressive Knochenlyse, Zerstörung der Nasenmuscheln und Conchae, Sinusitis, eine nasopharyngeale Raumforderung und regionale Lymphadenomegalie. Histologische und mikrobiologische Untersuchungen ergaben eine Infektion mit *Candida albicans*. Der Hund reagierte vorübergehend auf eine antimykotische Behandlung, wurde jedoch aufgrund einer klinischen Verschlechterung euthanasiert. Die pathologische Untersuchung bestätigte eine granulomatöse Pilzmeningitis und ein multizentrisches T-Zell-Lymphom.

Dies ist der erste Bericht einer granulomatösen Meningoenzephalitis bei einem Hund verursacht durch eine opportunistischen Candida-Infektion, die über bildgebende Verfahren diagnostiziert wurde. Der Hund in diesem Fallbericht zeigte eine aggressive Knochenlyse an derselben Stelle wie die Läsionen der granulomatösen Meningoenzephalitis, vergleichbar einer chronischen Candida-Infektion beim Menschen.

Schlüsselwörter: Lymphom, Cyclosporin, Immunsuppression, Hund, Pilz, Osteomyelitis

Summary

Opportunistic *Candida* infection of the central nervous system is increasingly observed in immunocompromised humans and has recently been reported in three dogs. Calvarial bone lysis is a rare manifestation of chronic *Candida* infection in humans but has not been reported in dogs.

This report describes the case of a 10-year-old immunocompromised Bullterrier dog with cerebral lesions associated with meningoencephalitis and multifocal aggressive bone lysis, destruction of turbinates and conchae, sinusitis, a nasopharyngeal mass, and regional lymphadenomegaly in MRI and CT. Histology and microbiological examinations revealed *Candida albicans* infection. The dog responded transiently to antifungal treatment but was euthanized due to clinical deterioration. Postmortem examination confirmed granulomatous fungal meningitis and multicentric T-cell lymphoma.

This is the first report describing imaging features of an opportunistic *Candida* infection causing granulomatous meningoencephalitis in a dog. The dog in this case report showed aggressive bone lysis at the same location as granulomatous meningoencephalitis lesions, a rare feature of chronic *Candida* infection in humans.

Keywords: lymphoma, cyclosporine, immunosuppression, canine, fungal, osteomyelitis

Introduction

Opportunistic *Candida* infection of the central nervous system (CNS) is an increasingly observed disease in immunocompromised humans[5,18–22] and has recently been described in dogs.[24,26] The literature describing the diagnostic imaging features of *Candida (C.) spp.* infection of the canine CNS is limited with one recent article describing multifocal intraaxial lesions within the forebrain of a dog observed with MRI.[24] The aim of this report is to contribute to the knowledge of the diagnostic imaging features of *Candida* CNS infection in dogs.

Case report

A female spayed 10-year-old Bullterrier dog was presented to the Zurich University Small Animal Hospital for a third opinion due to the reoccurrence of cluster seizures. Seven months prior to presentation the dog had been diagnosed with immune-mediated hemolytic anaemia and treated with immunosuppressive therapy (prednisolone 2 mg / kg every 24 hours; cyclosporin 5 mg / kg every 12 hours). Five months prior to the presentation at Zurich University Small Animal Hospital, the dog developed generalized tonic-clonic cluster seizures and a left-sided hemiparesis with a head tilt to the left. Blood examination showed severe neutropenia. A second veterinarian sent the dog to a human hospital for brain MRI, which revealed multifocal intra-axial lesions. Based on the imaging features and high serum titers Toxoplasmosis was suspected and the dog was treated with various antibiotics. One-month prior presentation at our clinic, the dog developed nasal discharge and deteriorated neurologically. The MRI was repeated at a veterinary referring center. Pachymeningitis was diagnosed and the dog was further immunosuppressed because of suspected idiopathic hypertrophic pachymeningitis. *Candida spp.* was found in a nasal smear and intranasal antifungal medication (Voriconazole) was started.

After a short initial improvement, the dog further deteriorated. Seven months after the onset of clinical signs the dog was presented for a third opinion at Zurich University Small Animal Hospital. The dog was treated with prednisolone (1,2 mg / kg / d), enrofloxacin, levetiracetam, inhalations with dexamethasone, gentamicin and voriconazole at the time of presentation. The dog showed serosanguinous nasal discharge, a cushingoid habitus, and generalized muscle atrophy. On neurological examination, the dog was apathetic, had left hemiparesis and was ambulatory only with sup-

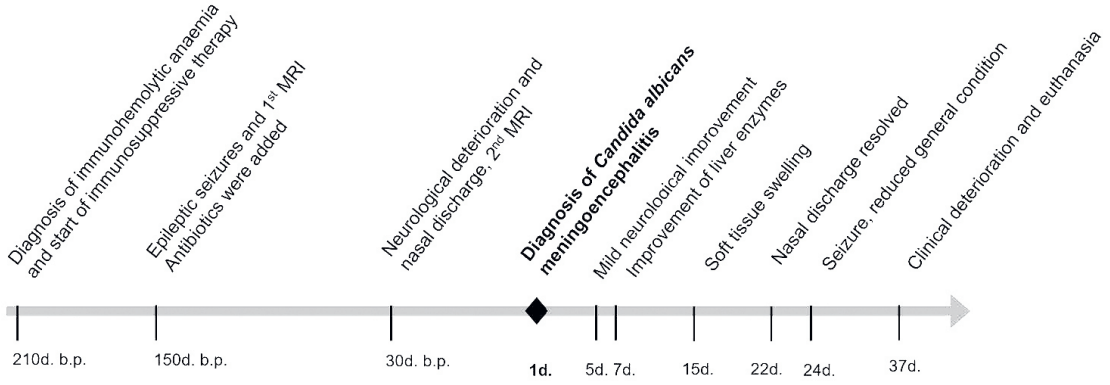

Figure 1: Historical information of dog's care presented in a timeline, d. = days, b.p. = before initial presentation to our hospital.

Table 1: Blood examination results performed in our hospital on the 1st, 7th and 15th days. HGB – hemoglobin, RBC – red blood cell count, RET – reticulocytes, ALP – alkaline phosphatase, ALT – alanine transaminase

	Reference values	1st day	7th day	15th day
Hematology	HCT 42 – 55 %	HCT 29	HCT 29	HCT 33
	HGB 14,4 – 19,1 g / dl	HGB 10,3	HGB 10,3	HGB 12,4
	RBC 6,1 – 8,1 *10E6 / µl	RBC 4,17	RBC 4,15	RBC 4,53
	–	RET 23769 / µl	RET 58100 / µl	–
Blood chemistry	ALP 20 – 98 U / l	ALP 3110	ALP 2244	ALP 3118
	ALT 20 – 93 U / l	ALT 1913	ALT 523	ALT 892

port. The menace response was inconsistent, and the pupillary light reflex was reduced bilaterally. Multifocal intracranial lesions including the right forebrain were suspected based on neurological examination.

Based on the history of prolonged immunosuppression and multifocal neurological signs, an infectious etiology was considered the primary differential along with neoplastic and immune- mediated causes. Blood examination results showed normocytic normochromic regenerative anemia and increased liver enzymes (Table 1).

Given the further clinical progression despite treatment, the patient underwent a repeated MRI examination (MRI protocol in Supplementary file, Table 1; 3 Tesla scanner, Philips Ingenia, Philips AG, Zurich, Switzerland). The MRI was performed under general anesthesia and intravenous gadolinium-based contrast agent (0,1 mmol / kg) was given.

The MRI examination revealed bilateral T2-weighted hyperintense, intra-axial lesions in the cingulate gyrus, olfactory bulb, and thalamus. The lesions affected predominantly the grey matter. They were mildly accentuated on the right

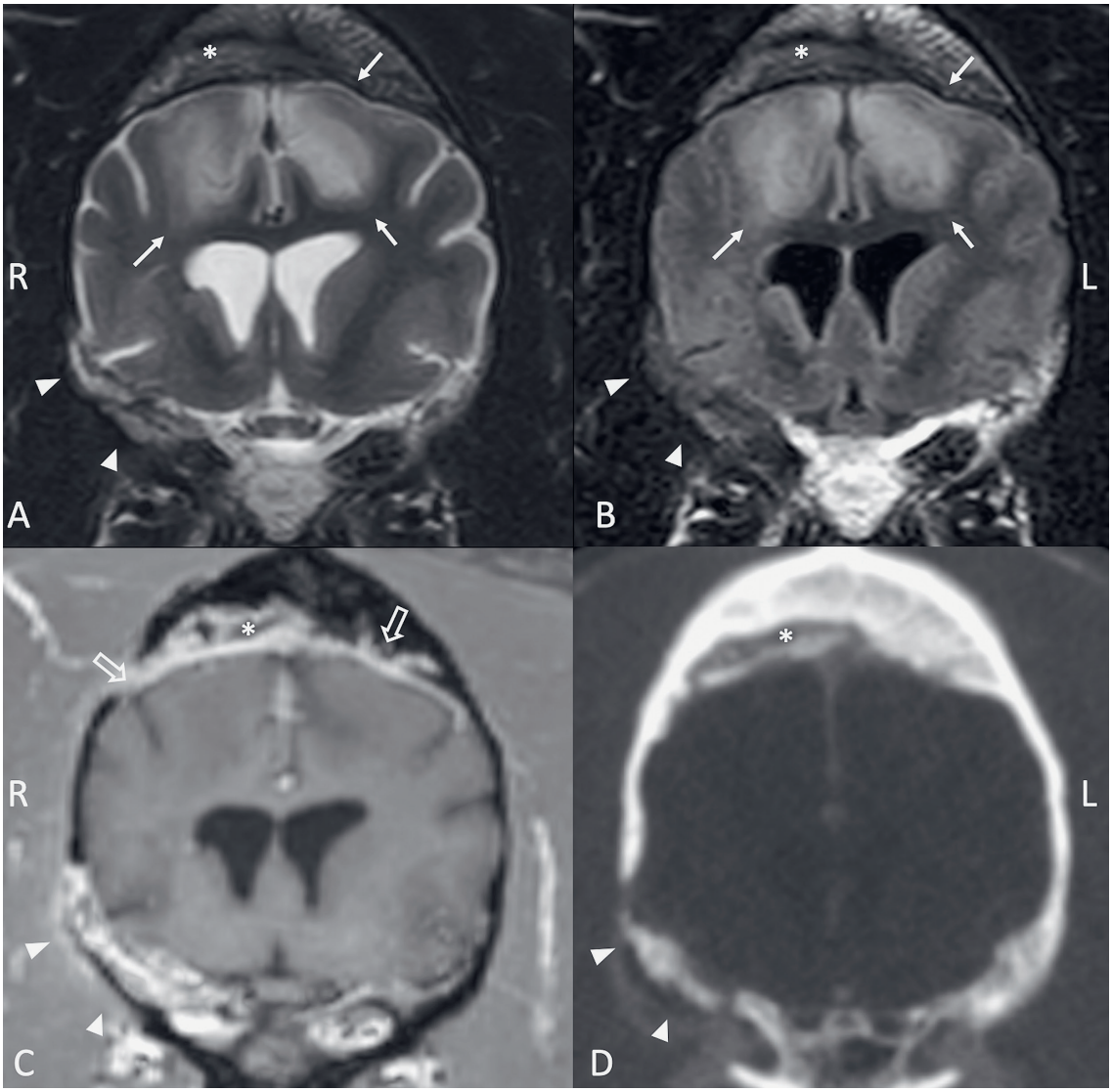

Figure 2: A: Transverse T2W, **B:** transverse T2W FLAIR, **C:** transverse T1W post-contrast and D: transverse reconstructed pre-contrast CT bone algorithm at the level of the orbital fissure.
Bilateral but accentuated right dorsal T2W and FLAIR hyperintense intra-axial lesions which did not show contrast enhancement (white arrows). Further intra-axial lesions were visible in the forebrain. Multifocal defects in the calvarium with associated T2W mixed and T1W hypointense material showing peripheral contrast enhancement (*). Concurrent mild to moderate predominately pachymeningeal thickening and contrast enhancement with extension into the soft tissues at the level of the bone defects (empty arrows). The CT image highlights the calvarial defects (white arrowheads).

side (Figure 2 A, B). These lesions were T1-weighted hypointense and mostly did not show contrast enhancement (Figure 2 C). Only the lesions in the olfactory bulb showed peripheral contrast enhancement towards the rostral meninges and cribriform plate. There were multifocal bone defects in the orbital portion of the frontal bone dorsal to the orbital fissure with concurrent mild to moderate predominately pachymeningeal thickening and contrast enhancement extending into the surrounding soft tissues (Figure 2 A, B and C, Figure 3 A).

Both frontal sinuses were filled with T2-weighted hyperintense material which showed moderate peripheral contrast enhancement. The delineation of the underlying bone and cribriform plate was reduced (Figure 3 A).

A heterogenous contrast enhancing lesion with a broad-based contact to the base of the skull was visible in the caudal nasopharynx. The right mandibular salivary gland was moderately enlarged with heterogeneous architecture and contrast enhancement.

There was marked bilateral enlargement of the regional lymph nodes with heterogeneous contrast enhancement and bilateral bulla effusion.

In conclusion there were multifocal intra-axial lesions in the forebrain with extensive pachy- and leptomeningitis, adjacent multifocal bone destruction and extension into the surrounding soft tissues. Mild destruction of turbinates and conchae, sinusitis with questionable integrity of the cribriform plate, a caudal nasopharyngeal mass and regional lymphadenomegaly with extension into the right mandibular salivary gland were visible.

Based on the multifocal distribution of the lesions affecting brain, bone, and soft tissue together with the progression of the lesions compared to the previous MRI examinations despite treatment, an atypical infectious agent or round cell neoplasia were considered the primary differentials. For better evaluation of the bone lesions and for disease staging a whole-body CT scan was performed (CT protocol in Supplementary file, Table 2; Philips Brilliance 16, Philips AG; Zurich, Switzerland) under the same general anesthesia.

The CT examination of the head confirmed multifocal moderate to marked aggressive bone lysis of the calvarium (Figure 2 D and Figure 3 B). Compared to the MRI the CT scan showed a larger extent of the bone lesions. There was a mild destruction of turbinates and conchae visible with sinusitis (Figures 3 A, B) which was underestimated in the

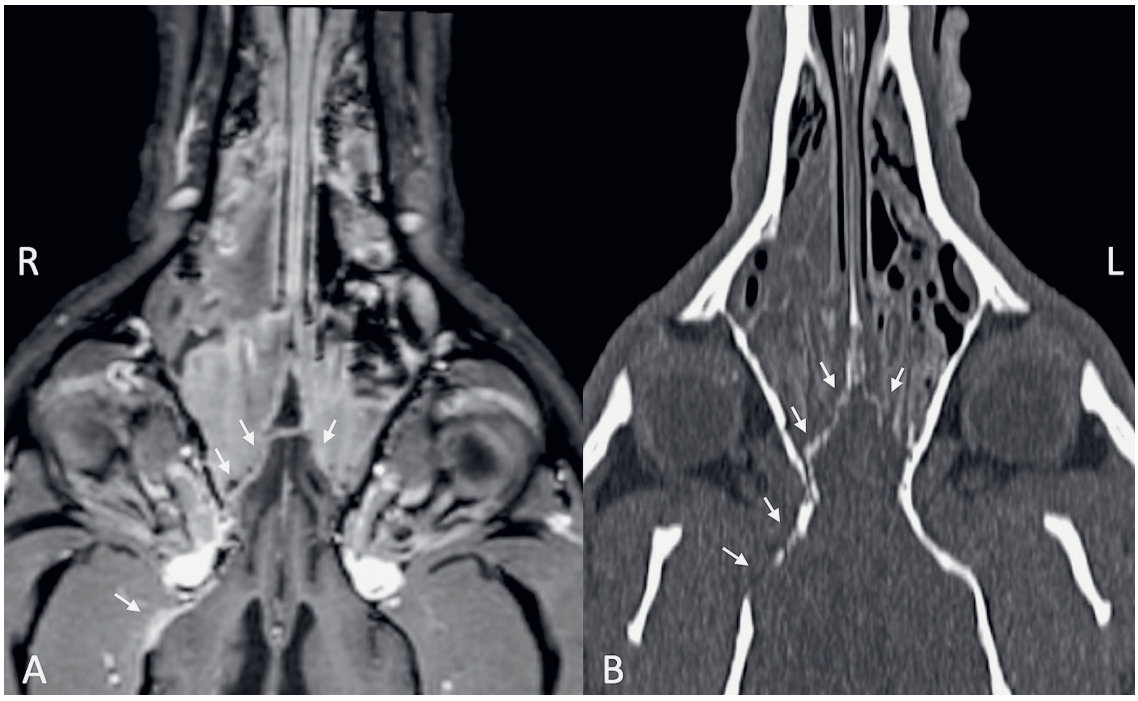

Figure 3: A: Dorsal T1W post-contrast and **B:** dorsal reconstructed pre-contrast CT image in a bone algorithm.
The CT image shows defects in the orbital portion of the frontal bone on the right side (white arrows).
Bilateral destruction of turbinates and conchae is visible along with small defects in the cribriform plate (white arrows).
The material in the nasal cavities is visible in MRI along with contrast enhancement at the level of the cribriform plate.
The defects in the cribriform plate are suspected in MRI but not clearly visible. The calvarial defects are more obvious in CT.

MRI examination but not associated with an empty nasal cavity. The suspected defects in the cribriform plate were confirmed by the CT examination. The remaining findings of the head were similar to the MRI findings. The CT scan of the remaining body revealed a nodular mass in the cranial abdomen, generalized lymphadenomegaly, moderate hepatomegaly, mineralization of the skin (calcinosis cutis) and multiple organs, also multifocal interstitial to alveolar pulmonary infiltrates. On the owners request no samples from these lesions were obtained.

Ultrasound guided fine needle aspiration was performed from the mandibular lymph nodes and salivary glands. Cytology examinations revealed reactive hyperplasia and mixed-cell inflammation. An atlantooccipital cerebrospinal fluid (CSF) tap was performed after imaging. The CSF was colourless and clear. The protein concentration (0,21 g / l, reference 0,3 g / l) and leucocyte count (0,5 leu / µl, reference 5 leu / µl) were within normal limits. CSF cytology was unremarkable, and CSF bacterial culture was negative. Serology for *Aspergillus spp.* was negative.

Samples were taken endoscopically from the nasopharyngeal mass for histological and bacteriological examination. They revealed multifocal infiltrating septate and branching fungal hyphae of *Candida albicans* with bacterial co-infection of *Enterococcus faecium*.

Treatment with systemic voriconazole (2,5 mg / kg every 12 hours) and isotonic NaCl inhalation was started. Prednisolone was reduced to 0,25 mg / kg every 12 hours. The nasopharynx and both frontal sinuses were surgically debrided and clotrimazole cream was instilled into the frontal sinuses. Five days after adjustment of the treatment the general condition of the dog improved, the dog became more alert and was ambulatory without support. The dog had mucopurulent nasal discharge and mucopurulent secretion from the trepanation site but was able to breathe normally with its mouth open. The blood examination on day 7 showed improvement of liver enzymes (Table 1).

Additionally, 15 d. after adjustment of the treatment the dog developed cytologically confirmed pyogranulomatous retropharyngeal and mandibular lymphadenitis with soft tissue swelling of the pharynx. Systemic antihistaminic medication (oral cetirizine 0,5–1 mg / kg) was started with a single intravenous injection of clemastine 0,05 mg / kg. Voriconazole blood level was 0,5 µg / ml (Institute of Clinical Chemistry, Zurich University Hospital), which was below the reference range of 1–6 µg / ml.[3] To reach described therapeutic blood level the voriconazole dose was doubled to 5 mg / kg every 12 hours (200 mg / d.). The nasal discharge resolved 22 days after the systemic voriconazole treatment was started, but progressive pharyngeal lymphadenomegaly caused upper airway obstruction with stridor. Hematology revealed improvement of erythrocyte count (Table 1). The voriconazole serum level increased above the reference range, trough 5,1 mg / l and peak after three hours 7,6 mg / l. Accordingly, voriconazole was reduced to 150 mg / d. Two days later the dog was again hospitalized because of a generalized tonic-clonic seizure and reduced general condition.

Thirty-seven days after diagnosis of candidiasis the dog showed progressive clinical deterioration with severe apathy, pale mucous membranes and non-ambulatory tetraparesis. The dog was euthanized by the referring veterinarian at the owner's request.

Subsequently the whole brain without calvarial bone was removed and fixed in 10 % formalin for histopathology and granulomatous meningitis was confirmed. The lesions were the most prominent at the area of the parietal cortex where fungal hyphae compatible with *Candida spp.* were observed (Figure 4 A, B). The cortex beneath the affected meninges showed chronic polioencephalomalacia (Figure 4 C). In addition, the frontal, parietal, and occipital cortices, and the underlying corona radiata were markedly and diffusely gliotic. A moderately well-demarcated area of leukoencephalomalacia involved the crus cerebri of the right thalamus and extended into the internal capsule and corona radiata (Figure 4 D).

Additionally, samples of kidney, liver, spleen, lung, lymph node and salivary gland were fixed in 10 % formalin and submitted for histopathology. Severe infiltration of a heterogeneous round cell infiltrate without fungal hyphae was observed in the salivary gland, liver and lung. Some of the infiltrating round cells had large pleomorphic nuclei with prominent nuclei and sparse cytoplasm. While infiltrating round cells multifocally expressed the B cell marker CD20, the T cell marker CD3 and the macrophage marker Iba-1 were only occasionally expressed. As immunohistochemistry could not clearly identify the aggressive infiltration of round cell neoplasia, PCR for Antigen Receptor Rearrangements (PARR) was performed (Genefast Laboratory, Forli, Italy), which revealed clonal amplification of T-cell receptors, consistent with T-cell lymphoma.

Discussion

Prevalence of fungal diseases depends partially on the geographical region.[1,4] *C. albicans* are ubiquitous fungi. Systemic candidiasis with CNS involvement in animals is rarely reported. In dogs, three case reports have been published describing vertebral *Candida* osteomyelitis without CNS involvement in a single case[10], as well as *C. albicans* granulomas in the brains of three dogs.[24,26]

Candida spp. are commensal organisms in the gastrointestinal tract, upper respiratory tract, along with the genital

mucosa of humans and animals. *C. albicans* is the most reported species causing human candidiasis and osteomyelitis[20–22] and is responsible for half of human candidiasis cases with CNS involvement. Hematogenous spread is the most common route of the CNS infection.[5,18,19] However, candidiasis remains rare and for a commensal organism such as *C. albicans* to become pathogenic systemic or local host defense mechanisms need to be compromised by virulent factors.[8,9,11] Risk factors that lead to compromise of the immune system and therefore increase the possibility of *C. albicans* crossing the blood-brain barrier (BBB), include chronic disease, neutropenia, neoplasia, treatment with corticosteroids, broad-spectrum antibiotics, and immunosuppressive drugs such as cyclosporine.[2,6–8,15,25,28] The dog presented in this report had been under long term treatment with immunosuppressive drugs including corticosteroids and cyclosporine. After the development of severe neutropenia, the dog additionally was treated with broad-spectrum antibiotics. These factors as well as multicentric lymphoma might have contributed to the systemic candidiasis in this

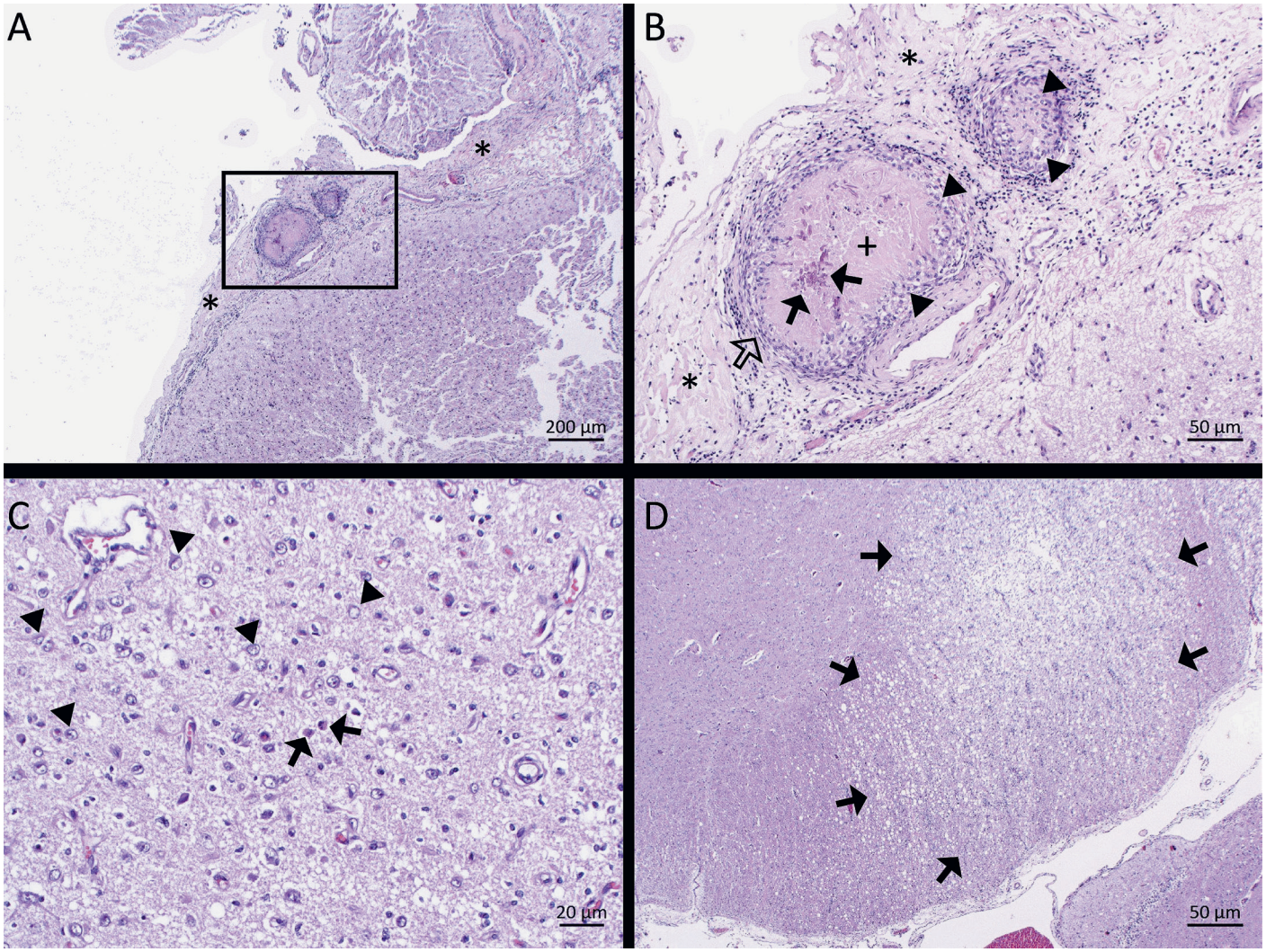

Figure 4: **A:** Right parietal cortex and overlying meninges. Two granulomas (black square) are located in the severely thickened and fibrotic overlying arachnoid membranes (*). The process slightly compresses the severely gliotic cortex (inset). The black square indicates the area shown in higher magnification in B. H&E, 20x magnification. **B:** The larger granuloma on the left contains eosinophilic elongated fungal hyphae (black arrows) within the central necrotic core (+) surrounded by epithelioid macrophages (black arrowheads) and a fibrous capsule (empty arrow). The smaller granuloma on the right is composed mainly of epithelioid macrophages (black arrowheads) and lacks central necrosis and fungal hyphae. The arachnoid membranes are highly thickened by fibrosis (*) and inflammation consisting of moderate numbers of lymphocytes and macrophages. H&E, 100x magnification. **C:** Higher magnification of the underlying parietal cortex showing diffuse astrocytic gliosis (large numbers of hypertrophic astrocytes with sparse to moderate amounts of eosinophilic cytoplasm, thick cell processes, and large open nuclei (black arrowheads)) and neuronal necrosis (black arrows) and loss. These changes are indicative of chronic polioencephalomalacia, H&E; 400x magnification. **D:** Crus cerebri. Large focal and moderately demarcated area of necrosis (leukoencephalomalacia), H&E, 100x magnification.

dog. Systemic candidiasis is less common than the focal form. Clinical signs depend on the organs affected, including fever, systemic lymphadenomegaly, osteomyelitis and meningoencephalitis, as seen in our case.[7,26]

Our case report describes systemic *C. albicans* infection presenting as granulomatous meningitis with concurrent lysis of the adjacent bone and the cribriform plate, as well as a space-occupying nasopharyngeal lesion. As *Candida spp.* are commensal organisms in dogs, positive cultures should be interpreted with caution. The typical gross appearance of white to yellow plaque formation on mucosal and serosal surfaces can be visible without infection.[29] In our case the infection in the meninges has been confirmed histologically. While pathology confirmed fungal infection in the meninges, no fungi were found in the intra-axial lesions. In humans and in dogs[24] *Candida spp.* typically forms micro abscesses at the junction of white and gray matters. *Candida spp.* may also form vascular lesions or may involve the leptomeninges.[5,18] In contrast, the intra-axial lesions in MRI in our case were compatible with polioencephalomalacia and leukoencephalomalacia without any detected fungal hyphae or abscesses. Therefore, polioencephalomalacia might be secondary to meningitis or might reflect post ictal changes rather than fungal encephalitis.[14] We could not determine an underlying cause for the leukoencephalomalacia. It might be secondary to undetected vascular disease or resolved inflammation that responded to corticosteroids.

Non-specific imaging features can delay the diagnosis and the treatment, which increases morbidity in human patients.[4,16] Diagnostic imaging features of CNS fungal diseases excluding candidiasis have been previously described in small animals and multifocal meningoencephalomyelitis, intracranial lesions that accompany sinonasal lesions should rase awareness for a possible fungal disease.[1] According to Nathan *et al.* the bone lysis is usually caused by large hyphae of *Aspergillus spp.* or *Zygomyces spp.* invading blood vessels, calvarium, and sinuses.[15] Therefore, in cases with more severe turbinate destruction and cribriform plate lysis aspergillosis is usually suspected, even though aspergillosis cases have been also reported without sinonasal lesions.[1] Serological examination to exclude a possible co-infection with *Aspergillus spp.* was performed in our case and showed a negative result. In our case bone lysis made the diagnosis of *Candida spp.* more challenging, as this feature is rare in candidiasis cases. MRI and CT scans of the head showed multifocal intra-axial lesions accentuated in the forebrain with severe meningitis. Adjacent extensive multifocal aggressive bone lysis of the calvarium and cribriform plate, destruction of turbinates and conchae, sinusitis, a heterogenous nasopharyngeal mass, and associated marked regional lymphadenomegaly were observed. Aggressive bone lysis without adjacent mass lesion is a rather rare finding in canine lymphoma.[12,13,17] In humans, like in dogs, lymphomas usually present as a solid soft tissue mass without aggressive bone destruction. Occasionally subtle patterns of tumor extension to the adjacent bone are seen.[23,27] In the present case lymphoma was one of differential diagnosis. However, tumor cells were not detected during the histopathological evaluation close to aggressive bone lysis. Instead, the mass lesion in the nasopharynx and granulomatous meningitis were consistent with the fungal disease. The diagnosis of invasive candidiasis is supported by the hyphae detected postmortem in the meninges and *Candida albicans* detected intravitam along with the negative *Aspergillus spp.* serology. In the author's opinion the lack of lymphoma cells and presence of granulomatous meningitis close to the lytic bone lesion makes it more likely that the fungal disease was also causing bone lysis. Unfortunately, calvarial bone was not sent for postmortem examination, precluding the proof of fungal invasion as the cause for the bone lysis.

The dog in our case deteriorated despite treatment. Failure to detect the T cell lymphoma during antemortem examinations might have contributed to the unsuccessful treatment in this patient.

Conclusion

This is the third report about opportunistic intracranial *Candida spp.* infection in dogs. Granulomatous meningitis, concurrent encephalomalacia associated with aggressive bone lysis and lack of abscesses are unique to this case.

Opportunistic *Candida spp.* infection should be considered as a differential diagnosis in immunocompromised dogs with meningitis accompanying sinonasal disease even in the presence of aggressive bone lysis.

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Infection opportuniste à *Candida albicans* avec méningo-encéphalite granulomateuse et ostéolyse agressive

L'infection opportuniste à *Candida* du système nerveux central est de plus en plus souvent observée chez les humains immunodéprimés et a récemment été rapportée chez trois chiens. La lyse osseuse crênienne est une manifestation rare de l'infection chronique à *Candida* chez l'homme, mais elle n'a pas été rapportée à ce jour chez le chien.

Ce rapport décrit le cas d'un Bullterrier de 10 ans, immunodéprimé, présentant des lésions cérébrales associées à une méningo-encéphalite et une lyse osseuse agressive multifocale, une destruction des cornets et des conques, une sinusite, une masse nasopharyngée et une lymphadénomégalie régionale à l›IRM et à la tomodensitométrie. L›histologie et les examens microbiologiques ont révélé une infection à *Candida albicans*. Le chien a répondu transitoirement à un traitement antifongique mais a été euthanasié en raison de la détérioration clinique. L'autopsie a confirmé la présence d'une méningite fongique granulomateuse et d'un lymphome T multicentrique.

Il s'agit du premier rapport décrivant les caractéristiques d'imagerie d'une infection opportuniste à *Candida* causant une méningite granulomateuse chez un chien. Le chien dont il est question ici présentait une lyse osseuse agressive au même endroit que les lésions de méningo-encéphalite granulomateuse, un cas rare lors d'infection chronique à *Candida* chez l'homme.

Mots clés: lymphome, cyclosporine, immunosuppression, chien, champignon, ostéomyélite

Infezione opportunistica da *Candida albicans* con meningoencefalite granulomatosa e osteolisi aggressiva

L'infezione opportunistica da *Candida* nel sistema nervoso centrale è sempre più osservata negli esseri umani immunocompromessi ma è stata recentemente riportata anche in tre cani. Tuttavia, nei cani non è ancora stata diagnosticata la manifestazione di osteolisi del cranio, che talvolta si verifica negli esseri umani, in caso di infezione cronica da *Candida*.

Questo studio descrive un Bull Terrier di 10 anni, immunocompromesso, con lesioni cerebrali associate a meningoencefalite, lisi ossea multifocale aggressiva, distruzione dei turbinati e delle conche nasali, sinusite, una massa rinofaringea e linfoadenomegalia regionale evidenziate tramite risonanza magnetica (MRI) e tomografia computerizzata (CT). Gli esami istologici e microbiologici hanno confermato un'infezione da *Candida albicans*. Il cane ha risposto momentaneamente al trattamento antifungino ma è stato sottoposto a eutanasia a causa del peggioramento clinico. L'esame patologico ha confermato una meningite fungina granulomatosa e un linfoma T multicentrico.

Questo è il primo caso di una meningoencefalite granulomatosa in un cane causata da un'infezione di Candida, diagnosticata tramite imaging. Il cane di questo studio ha mostrato una lisi ossea aggressiva nella stessa sede delle lesioni della meningoencefalite granulomatosa, una caratteristica rara anche nell'infezione cronica da Candida negli esseri umani.

Parole chiave: linfoma, ciclosporina, immunosoppressione,w cane, fungina, osteomielite

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