Atypical sphenoid bone osteomyelitis in a maltese dog caused by cryptococcosis: a case report

M. Kwiatkowska¹, A. Pomianowski¹, Z. Adamiak¹, I. Otrocka-Domagala¹, T. Widawski², K. Pazdzior¹

¹Veterinary Medicine Faculty, University of Warmia and Mazury, Olsztyn, Poland
²GE HealthCare, Euromedic Diagnostics, Olsztyn, Poland

ABSTRACT: This article describes osteomyelitis of the sphenoid skull bone in a maltese dog due to Cryptococcus neoformans var. neoformans infection. The affected dog was subjected to physical and neurological examinations. Complete blood count (CBC), biochemistry profile, lymph node biopsy, cerebrospinal fluid (CSF) examination were also performed. This case report describes abnormalities in magnetic resonance imaging (MRI) examination as well as the histopathologic lesions of the skull bones and neurological symptoms of the dog.

Keywords: dog; blindness; ataxia; sphenoid bone osteomyelitis; cryptococcosis

List of abbreviations

CBC = complete blood count, CSF = cerebrospinal fluid, FLAIR = fluid attenuated inversion recovery, HE = hematoxyline and eosine, MRI = magnetic resonance imaging, SBO = sphenoid bone osteomyelitis, WBC = white blood cells

Cryptococcus neoformans is a saprophytic, yeast-like organism. The most often reported route of infection is inhalation of the uncapsulated organism and a predilection for the central nervous system has been noted. Neurological signs are associated with lesion localisation. The disease requires long treatment, but the course is often fatal.

In human medicine typical cases of SBO are induced by malignant or advanced stages of ear infection with Pseudomonas aeruginosa as an underlying pathogen. The typical form of SBO usually occurs in older patients with immunodeficiency, diabetes mellitus, HIV infection, or chronic sinus inflammatory disease. The atypical form of SBO is less frequent and is usually caused by fungi infections like Mucor spp., Aspergillus spp., Cryptococcus spp. or by coexisting Staphylococcus spp., Salmonella, Mycobacterium, Pseudomonas infections (Grobman et al., 1989; Parker et al., 1996; Kountakis et al., 1997). In dogs osteomyelitis usually affects the appendicile skeleton (Caywood et al., 1978). Similarly as in human medicine it may be a result of periodontal disease, otitis media and externa or bite wounds. Osteomyelitis which affects the skull has been described by Stead (1984), but no details concerning the affected bones were mentioned. Osteomyelitis of unknown origin was reported in a Great Dane by Grabh et al. (1995). In 2009 a sphenoid bone osteomyelitis of unknown aetiology causing visual impairments has been reported in two Springer Spaniels, a Golden Retriever and in one Domestic Long Haired cat (Busse et al., 2009).

In this article we present a case report of SBO in a 16-month old maltese dog with respiratory, visual, and neurological deficits due to cryptococcosis infection.

Case description

A 16-month old Maltese, male dog was referred to the Small Animal Hospital of Internal Medicine.
at the Department of Veterinary Medicine faculty in Olsztyn, Poland for evaluation of the upper respiratory tract and neurological signs.

The dog had been acquired by the owner as a puppy from the breeder and had lived only in Olsztyn. It was regularly vaccinated and received a preventative against internal and external parasites. The dog had a history of previous upper respiratory disease symptoms like catarrh, fever, and enlarged submandibular lymph nodes within the previous three months. The dog had been treated with the antibiotic amoksycyline with clavulonic acid and non-steroidal anti-inflammatory drugs. After initial treatment the dog improved; unfortunately however, the respiratory symptoms returned and the dog started showing neurological signs like ataxia and visual deficits. The dog was then administered Cephalexin (Ceporex®, Schering plough, Poland) s.c. at 30 mg/kg of body weight and dexamethasone (Rapidexon®, Novartis, Poland) at 0.5 mg/kg of body weight i.v. Despite initial improvement the neurological signs deteriorated.

At the time of referral the dog was mentally obtunded, but responsive. Gait examination revealed ataxia of all four limbs and front limb hypermetria. Torticollis and drifting to the left was noticed. Propriocceptive deficits were present on four limbs. The dog showed symptoms of pain when palpated in the region of the atlas, suggestive of meningoencephalitis. Intension tremors were noticed. Ophthalmologic examination revealed mydriasis in both eyes, ventral strabisumus of the left eye and spontaneous nystagmus. The menace reflex was absent. Fundic examination revealed a chorioretinitis, and retinal granulomatous lesions bilaterally. Examination of the other cranial nerves revealed no abnormalities.

At clinical examination the dog was normothermic (37.8 °C) and tachycardic (135 beats/min), and was panting which might have been due to stress. The submandibular lymph nodes were of plum size, whereas popliteal was of an almond size. A CBC and biochemistry profile was performed. The WBC were in the reference range (11.4/µl, reference range 5.2–13.9 × 10³/µl), whereas the monocytes were slightly elevated (3.21 monocytes/µl; reference range 1.35–1.50 monocytes/µl). Results of serum biochemical analyses were unremarkable, although alanine transaminase and alkaline phosphatase levels were slightly elevated (respectively 135 IU/l, 231 IU/l). Due to progressive neurological signs the decision to perform an MRI examination was made. The dog was premedicated with atropine at 0.005 mg/kg and medetomidine (Domitor®, Pfizer Animal Health Australia) at 0.02 mg/kg. Anaesthesia was maintained with propofol (Plofed®, Polfa S.A., Poland) in bolus at 5 mg/kg of body weight. The dog was intubated and anaesthesia was maintained with 4 mg of propofol per kg/h. MRI was performed in sternal recumbency with the use of a dog head coil on a 0.25 Tesla Vet Grande (Esaote, Italy) low field magnet. The examination was made in the sagittal, transverse and coronal planes. The protocol included T1-, T2-weighted images in Fast spin echo (FES REL–TR 5440 ms, TE 90 ms, slice thickness 3 mm, interslice gap 0.5 mm), fluid attenuated recovery (FLAIR–TR 6610 ms, TE 100 ms, TI 1250 ms, slice thickness 3 mm, interslice gap 0.5 mm), short tau inversion recovery (STIR–TR 4470 ms, TE 100 ms, TI 80 ms, slice thickness 3 mm, interslice gap 0.5 mm), gradient echo (GE STIR 3D–TR 300 ms, TE 16 ms, TI 70 ms, slice thickness 2.8 mm, interslice gap 0.5 mm), and pre and post IV contrast (0.15 mmol/kg of body weight gadodiamidum – Omniscan 0.5 mmol/ml, GE Healthcare, Ireland) spin echo (SE–TR 720ms, TE 18 ms, slice thickness 3 mm, interslice gap 0.5 mm).

MRI examination revealed a sphenoid bone mild hypointensity in T1W images (Figure 1), whereas on T1W images post contrast an abnormal enhancement of the sphenoid bone was visible adjacent

Figure 1. Transvers T1W image, a hipointensity of sphenoid bone (blue arrow) in comparison to other skull bones hiperintensity (red arrow)
of extraocular muscles and fat tissue was noted, after contrast administration diffuse enhancement was observed in the T1W image. In the T2W (Figure 3) image the sphenoid bone was slightly hypointense in comparison to the normal fatty bone marrow. FLAIR revealed an enhancement of the meninges signal and increased conspicuity of lesions around the sulcus resulting from CSF attenuation.

Following the MRI results CSF examination was performed. To this end, a sample was obtained from the cerebromedullary cistern. The fluid was characterised by high protein concentration 90 mg/dl (reference range < 25 mg/dl), and nucleated cell count was increased at 15 cells/ml (reference range 0–4 nucleated cells/ml) with 50% of neutrophils, 26% of macrophages, 14% of lymphocytes and 10% of eosinophiles. No blood contamination was evident. In the smear, macrophages with fungal organisms were indentified. Simultaneously, a percutaneous lymph node fine needle biopsy was performed. HE staining revealed the presence of fungi. It was decided to excise one of the submandibular lymph nodes. Histopathological examination and India Ink staining revealed Cryptococcus infection.

Antifungal treatment with itraconazole (Itra-Merck®, Generics, UK) at a dose of 10 mg/kg p.o. BID was started. Due to meninoencephalities the prednisone was administered in a dosage of 0.1 mg/kg of body weight.
Despite the administration of the antifungal treatment, the condition of the dog deteriorated. Within two weeks the owner reported that the dog could not stand or walk. It was also vocalising and pacing in circles. Short 15-second seizure episodes were observed. The dog was administered a single dose of mannitol (Mannitol 20% Fresenius®, Kabi, Poland) in a dose of 0.5 g/kg i.v. To prevent further seizures gabapentine (Gabapentin®, Teva pharmaceuticals Poland) in the dosage of 10 mg/kg of body weight was administered p.o. BID. Gabapentine was used due to its minor sedative effect. Unfortunately, the neurological status of the dog became more severe and the dog started to be comatose. The decision to euthanize the dog was made.

During necropsy, samples of the brain, cerebellum, sphenoid bone and ethmoid bone were taken for histopathologic examination. A routine hematoxylin-eosin (HE) stain was performed. In the brain, cerebellum and leptomeninges, the accumulation of numerous yeast-like organisms (Cryptococcus neoformans) of various sizes, with foamy or bubbly appearance and congestion were observed (Figure 4). The organisms were oval to spheroid (2 to 10 µm in diameter), sometimes crescentic or cup shaped, and were surrounded by a thick region of non-staining in the HE stain capsule which appeared like a clear halo (Figure 5). There were scant or no inflammatory reactions visible. In the sphenoid and ethmoid bones, atrophy of the trabeculae and medullary cavity expansion with yellow bone marrow aggregation were noticed (Figure 6). Diffuse accumulations of Cryptococcus neoformans var. neoformans organisms were visible in the medullary cavity, especially in the sphenoid bone (Figure 7). The fungal osteomyelitis was not accompanied by the infiltration of inflammatory cells.

DISCUSSION AND CONCLUSIONS

In human medicine sphenoid bone osteomyelitis is uncommon (Singh et al., 2005). Usually it spreads from a malignant ear infection through the ear canal. The main isolated pathogen is Pseudomonas aeruginosa and the disease occurs mainly in immunocompetent patients (diabetes mellitus, glicocorticosteroids administration), or as a complication of inadequate treatment for otitis...
The atypical form of SBO may also originate from sinonasal bacterial infections with *Staphylococcus*, *Pseudomonas*, *Salmonella* or fungi infections with *Aspergillus*, *Mucor*, *Aspergillosis* (Grobman et al., 1989; Parker et al., 1996; Kountakis et al., 1997), and is not a complication of otitis interna. We assume that our clinical case is an atypical form of SBO elicited by *Cryptococcus* infection, which originated from a prior sinonasal infection.

Individuals infected with *Cryptococcus neoformans* often present with symptoms of headache, fever, facial swelling, and sinusitis. Our patient showed symptoms of sinusitis for two months. The dog was irritable while the owners were playing with him or cuddling him, which is consistent with the headache symptom commonly reported in people. Similarly as in human medicine reports the dog was obtundant, which may have been associated with septic thrombosis of major intracranial vessels (Wong and Quint, 1999). The concomitant symptoms like ataxia, paresis, hypermetria, mydriasis, and nystagmus are characteristic for multifocal neurological disease. Clinical signs are usually connected to lesion location (Lavely and Lipsitz, 2005).

Atypical SBO secondary to fungal infection occurs usually in immunocompetent people. We believe that it is possible that our patient was immunocompetent or immunosuppressed. Moreover the dog was receiving glucocorticoids (dexamethasone, prednisolone) as treatment for upper respiratory tract diseases when the neurological signs were observed. After administration a quick but short-lasting improvement was noted, and the condition of the dog subsequently deteriorated.

Among diagnostic imaging techniques MRI examination is a preferred choice in both human and veterinary medicine, due to its sensitivity, superior resolution, and multiplanar capabilities (Wong and Quint, 1999).

As in human medicine (Wong and Quint, 1999), the T1W sequence was in our study very sensitive to minor pathologic changes in the skull base. In humans the most consistent finding of SBO in MRI examination is a loss of T1W signal hyperintensity of the skull base marrow fat (Singh et al., 2005). The T1W image of our dog revealed a mild hypointensity of the sphenoid bone in comparison to normal fatty bone marrow. Busse et al. (2009) reported that in all of their patients the sphenoid bone was more significantly hypointense than in our clinical case. The fungal body is composed of iron and manganese; these compounds cause varying signals: from hyperintensity in T2W to hypointensity in T1W and T2W images, especially when concerning sinuses and skull bones (Grabh et al., 1995). We are of the opinion that the difference in MRI signal in our case in comparison to Busse et al. (2009) is due to massive fungal accumulation in the bone.

In our case the frontal, nasal sinuses were hyperintense in the T2W image. Histopathologic examination revealed *Cryptococcal sinusitis* with multiple fungal organisms. Administration of paramagnetic contrast medium revealed a marked enhancement of sphenoid bone, meninges, and extraocular muscles. A mild exophthalmus might have been caused due to diffuse swelling of extraocular masses and fat tissue.

Fungal bone invasion is uncommon (Grobman et al., 1989; Lancaster et al., 2000; Chang et al., 2003; Singh et al., 2005), because it is the tissue invaded last by fungi. Therefore, the SBO must have been due to the angioinvasiness of *Cryptococcus neoformans* var. *neoformans* and its ability to extend through the soft tissue supplying the blood vessels, and the orbit and optic nerve. In our case, histopathologic examination confirmed fungal invasion of the orbit, optic chiasm and optic nerve, which are in a close proximity to the sphenoid bone. In the sphenoid bone multiple fungal organisms were detected, and atrophy of the trabeculae with expansion of the medullary cavities together with yellow bone marrow aggregation was observed.

In humans the atypical form of SBO is usually centred on the sphenoid and occipital bones rather than the temporal bone (Chang et al., 2003), which is consistent with our findings. In the era of antibiotic therapy the involvement of the orbit and optic nerve in humans is very rare (Holder et al., 1986). In our patient the optic nerve and optic chiasm were also infected. To our knowledge the dog had never suffered from otitis externa.

In human medicine MRI examinations as well as a gallium 67-imaging are extremely helpful in monitoring the progress of treatment (Parker at al., 1996). We assume that this would also be useful in veterinary medicine, but unfortunately we did not have the opportunity to test this, due to euthanasia.

Cryptococcal meningitis is usually a slow-progressing chronic disease (Wong and Quint 1999), which was the case in our study. Sometimes the disease can be fulminant and rapidly fatal.
Intracranial lesions characteristic for Cryptococcal infections include perivascular “soap bubble”, granulomas, fibrogranulomatous masses, gelatinous masses, and mixed forms. In immunocompetent human patients, who are not able to mount a normal inflammatory response, Cryptococcus neoformans var. neoformans can multiply very rapidly usually forming gelatinous lesions. We observed the same lesions in histopathologic examination. For the most part, no inflammatory response was noticed, apart from mild meningies infiltration. In humans cryptococcosis gelatinous lesions are isointense to slightly hypointense on T1 weighed images, and hyperintense in T2 weighed images. In our examination the lesions were isointense in the T1 weighed image, and hyperintense in the T2 weighed image.

REFERENCES


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