COMPANION OR PET ANIMALS

Successful treatment of chronic canine blastomycosis in a Labrador retriever with sterile histopathology

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SUMMARY

A four-year-old, neutered male Labrador retriever from Minnesota, USA was presented to a dermatology referral clinic for evaluation of waxing and waning paronychia and multifocal cutaneous nodules of five months' duration. The condition was managed before referral with antibiotics and glucocorticoids resulting in a partial response, but new lesions continued to develop. Skin biopsies made both before and after referral revealed pyogranulomatous dermatitis and fibrosis with negative fungal stains. However, acetate tape impression cytology performed at time of referral detected a single blastomyces organism; thus, a definitive diagnosis of blastomycosis was made. Treatment with fluconazole followed by generic itraconazole resulted in rapid, full recovery in three months' time. Thoracic radiographs at the time of blastomycosis diagnosis were within normal limits, despite history of mild cough. This case highlights the potential pitfalls in diagnosis and treatment of canine blastomycosis.

BACKGROUND

Blastomycosis is a systemic fungal infection that occurs in almost all mammalian species, most commonly dogs and human beings (Werner and Norton 2011). Clinical manifestations are highly varied and range from mild to life-threatening disease and may be acute, subacute or chronic. Blastomyces dermatitidis exists in the soil as a thermally dimorphic fungus (Choptiany and others 2009). Infection may occur worldwide but is endemic to certain ecological niches such as the Mississippi, Missouri and Ohio river valleys in the USA and south-eastern Canada. Environmental factors such as acidic or sandy soil, decaying wood, humidity and proximity to waterways have been implicated as risk factors for infection. Patient risk factors include young age, breed (Dobermans, golden retrievers and Labrador retrievers) and male sex (Archer and others 1987, Rudmann and others 1992, Werner and Norton 2011). Susceptible hosts are typically infected via inhalation of aerosolised conidia released from mycelia upon soil disruption. Within the lungs, conidia convert to thick-walled budding yeast that can be disseminated haematogenously or lymphatically to the skin, bones, central nervous system and eyes (Choptiany and others 2009, Werner and Norton 2011). Uncommonly, direct dermal inoculation may occur causing localised granulomatous disease (Werner and Norton 2011). Dogs and their owners may acquire blastomycosis simultaneously after exposure to a common source (Choptiany and others 2009). However, as the fungus is not transmissible between human beings, between animals, or from animals to human beings, it is neither zoonotic nor contagious (Werner and Norton 2011). The case presented here is typical in regards to its dermatological presentation, but is unique due to absence of radiographic pulmonary pathology and absence of identifiable blastomyces organisms on multiple histopathology specimens, even with special fungal staining techniques.

CASE PRESENTATION

A four-year-old, neutered male Labrador retriever from west-central Minnesota, USA presented for evaluation of waxing and waning skin lesions of nearly five months' duration. The patient had a one-year history of intermittent dry cough and decreased appetite; there was no previous history of pruritus, skin or ear disease. The patient had access to wooded outdoor areas and spent time swimming in various waterways. Skin lesions began as moist interdigital erythema of the rear feet and as a draining nodule on the dorsal lumbar area. Initially, partial response was achieved with 1000 mg oral cephalexin twice daily and 20 mg oral prednisone once daily tapering. However, after one week, lameness and moderate swelling of the tarsus and fifth digit developed. Cephalexin and prednisone were discontinued and 500 mg oral amoxicillin twice daily and 100 mg oral carprofen once daily were initiated. Despite treatment, swelling progressed and new draining tracts developed on the left lateral metatarsus. Additionally, the claw from the most severely affected digit sloughed. Complete blood count (CBC) showed mild leucocytosis and cytology of the skin lesions showed red blood cells, a pleomorphic population of white blood cells, and no infectious organisms. The lesions waxed and waned despite additional antibiotics and periodic administration of prednisone. By day 101, digit lesions had improved but there was linear thickening of the skin and subcutaneous tissues on the left rear leg with draining tracts and new skin lesions on the dorsum and left shoulder. Chemistry panel showed mild elevation in alkaline phosphatase (297 U/L, Reference Intervel [RI] 20–150). Aerobic bacterial culture of an area of exudation was negative. Histopathology of a draining area on the left rear leg and dorsum revealed multifocal pyogranulomatous folliculitis and furunculosis with fibrosis, and special stains for fungal organisms were negative. At this time, the patient was referred to the authors' dermatology practice for further diagnostics and treatment recommendations.

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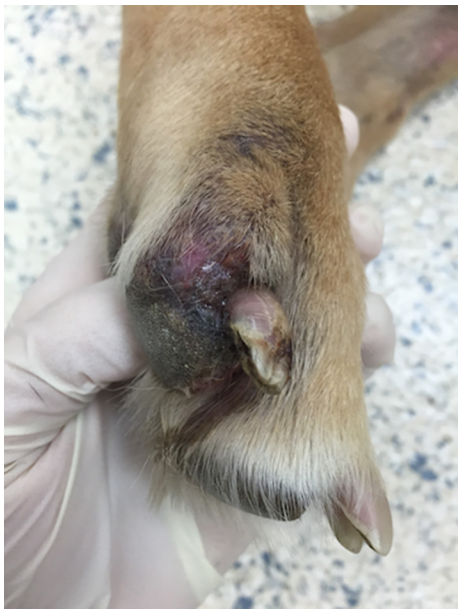

FIG 1: Paronychia on right rear fifth digit from a four-year-old Labrador retriever with blastomycosis.

On presentation, the right rear fifth digit had moderate paronychia, mild patchy alopecia and onychorrhexis (Fig 1); slight purulent drainage was present adjacent to the lateral nail-bed. The left rear fifth digit had moderate paronychia, mild patchy alopecia and onychodystrophy. Multifocal nodules between 0.5 cm and 2.5 cm were present on the trunk and on all four limbs (Fig 2). Focal, approximately 0.4 cm, erythematous, slightly raised to nodular lesions with central erosion were present on the upper lip margins bilaterally. The trunk additionally had at least ten 0.5–1 cm diameter patches of alopecia with thin overlying tan crusts. There was mild erythema of both pinnae, a prominent left axillary peripheral lymph node and cardiopulmonary auscultation was normal.

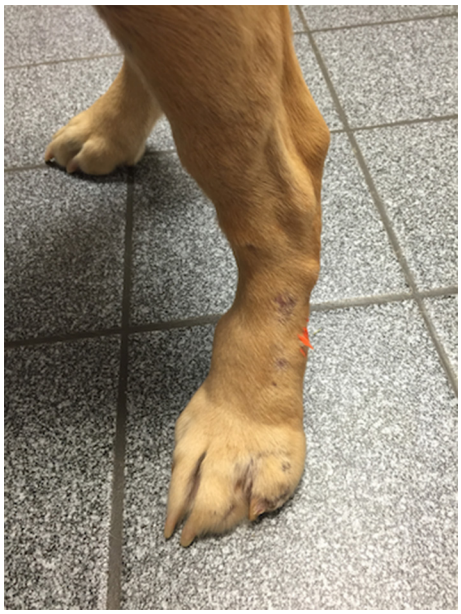

FIG 2: Distal left rear limb of a four-year-old Labrador retriever with blastomycosis showing nodular dermatitis, patchy alopecia and onychodystrophy of the fifth digit.

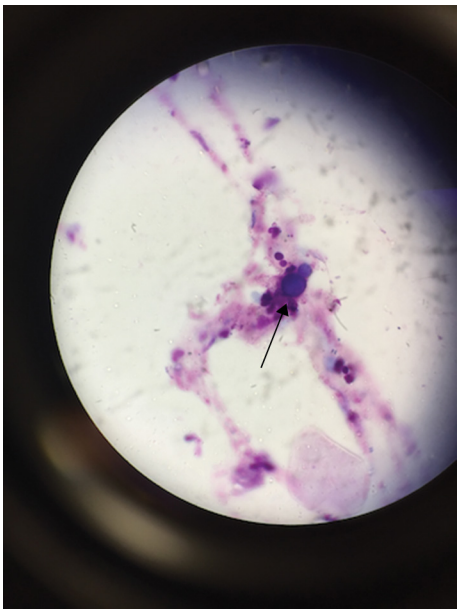

FIG 3: Cytological examination of exudate obtained via direct acetate tape impression from the right rear fifth digit of a four-year-old Labrador retriever revealed a single, large, broad-based budding yeast organism consistent with Blastomyces dermatitidis.

INVESTIGATIONS

A direct impression smear was performed on exudate draining from the right rear fifth digit and revealed large numbers of coccoid bacteria with accompanying pyogranulomatous inflammation. Direct acetate tape impression of the skin lesions revealed coccoid bacteria, neutrophils and a single, large, broad-based budding yeast organism consistent with Blastomyces dermatitidis (Fig 3). A fine needle aspirate of a skin nodule on the left rear leg revealed pyogranulomatous inflammation and rare coccoid bacteria. CBC revealed mild monocytosis (896/uL, RI 0–840), chemistry profile was within normal limits and urinalysis had specific gravity 1.030 (RI 1.015–1.050), pH 8.5 (RI 5.5–7.0), 1+ proteinuria (RI negative), inactive sediment and microalbuminuria of 0.5 mg/dL (RI<2.5 mg/dL). Thoracic radiographs were within normal limits. Fungal cultures were not pursued due to the significant human health risk posed by the mycelial form of Blastomycosis dermatitidis growing in the laboratory. Punch biopsy under local anaesthesia was performed of the draining tract on the right rear fifth digit and of a nodule overlying the left lateral tarsus. The histopathological diagnosis was pyogranulomatous dermatitis with fibrosis and periodic acid-Schiff (PAS) stain for fungal organisms was negative. A urine Blastomyces antigen test was advised but declined due to cost and the positive detection of a Blastomyces yeast on tape impression.

DIFFERENTIAL DIAGNOSIS

A young, large-breed dog with draining, nodular skin disease may have a systemic fungal infection, sterile granulomatous disease, sterile nodular panniculitis, reactive histiocytosis, neoplasia, actinomycosis, mycobacteriosis, nocardiosis, parasitic disease or deep pyoderma. These conditions cannot be differentiated based on clinical appearance alone. Routine treatment of autoimmune disease with glucocorticoids is in direct opposition to the treatment for systemic infectious dermatoses which could fulminate upon immunosuppression leading to significant

patient morbidity and possibly mortality. Biopsy with special stains (such as PAS, Grocott-Gomori's methenamine silver (GMS) or Fite's acid fast) is often a reliable method to differentiate but is not a perfect test. The historical environmental details of this case, including the patient's signalment, lifestyle, and residence in a blastomycosis endemic region and the lack of a complete response to glucocorticoid treatment and multiple antibiotics made the suspicion of fungal infection all the greater.

TREATMENT

Pending histopathology confirmation, the patient was prescribed 1200 mg oral cephalexin twice daily for 30 days, 300 mg oral fluconazole once daily and 4% chlorhexidene surgical scrub topical to draining lesions twice daily.

OUTCOME AND FOLLOW-UP

The skin lesions had improved dramatically within four days of treatment initiation. By day 11, biopsy sites were healed and the skin lesions noted at initial presentation were quickly resolving. However, the owner noted development of several new nodules overlying the shoulder region. At this time, treatment was changed from fluconazole to 300 mg oral generic itraconazole once daily due to the appearance of the new nodules and in an attempt to shorten the total treatment duration. After two months of itraconazole treatment, the rear limbs, which had been so severely affected previously, appeared normal.

The owner discontinued itraconazole treatment after 60 days. At the time of writing, 284 days after presentation to the authors' clinic, the patient is doing well with no recurrence of skin nodules or paronychia.

DISCUSSION

Blastomycosis is frequently multisystemic with varied clinical signs dependent on the organ affected, fungal load and individual host response to infection. Of 115 dogs diagnosed with blastomycosis in a Louisiana, USA study, 88% had respiratory, 67% lymphatic, 52% ocular, 52% cutaneous, 12% bone and 6% CNS involvement (Arceneaux and others 1998). Many aspects of the case described herein are typical findings including the history of cough, pyrexia, decreased appetite, decreased activity level and the appearance of multiple nodular draining skin lesions (Greene 2013). However, this case presented a diagnostic challenge to definitively diagnose Blastomyces yeast as the causative agent for the clinical disease. Additionally, the apparent initial response to glucocorticoid and antibiotic treatment further delayed the diagnosis.

The gold standard for diagnosis of blastomycosis is a combination of clinical signs and demonstration of the causative organism on cytology or histopathology (Spector and others 2008). Round to oval yeast cells 8–15 micrometers with a single broad-based bud and thick, refractile cell walls may be seen (Saccente and Woods 2010) but negative cytology does not rule out infection (Spector and others 2008). In this case, numerous cytological samples utilising different techniques allowed identification of a single organism from a draining skin lesion. Cytology is an important, inexpensive tool in the evaluation of dermatology cases. In the case presented herein, failure to fully evaluate this patient cytologically would have been detrimental, as a definitive diagnosis would likely not have been reached.

Confirmation of blastomycosis was attempted via histopathology. This aspect of the case is a particularly important learning point as it can be easy to assume that histopathology is a more important diagnostic tool than history, physical examination or in-house diagnostics. The patient of this report had multiple skin lesions biopsied on two separate occasions. Two experienced histopathologists evaluated the samples and the morphological diagnoses of pyogranulomatous dermatitis, furunculosis and fibrosis are consistent with blastomycosis infection (Wehner and others 2008). Visualisation of fungal organisms on histopathological sections can be enhanced by PAS with haematoxylin counterstain or GMS staining (Saccente and Woods 2010). Special stains in the case described herein were negative for fungal organisms.

The protracted mild disease and paucity of organisms in the present case, especially considering the intermittent steroid treatment, is very unusual and deserving of further discussion. Host factors may partially explain this outcome, such as a robust cell-mediated immunity which is essential to preventing progression of infection (Saccente and Woods 2010). Although uncommon, occasional dogs from endemic regions may develop subclinical disease with spontaneous resolution (Klein and others 2000) or recover from symptomatic blastomycosis without treatment (Arceneaux and others 1998). It should be noted that spontaneous resolution is exceedingly rare, and dogs presenting with clinical symptoms of blastomycosis should be treated (Kerl 2003). However, considering the low number of organisms in the present case, it is possible the dog would have cleared the infection without treatment if given more time. It is also possible that the intermittent steroid treatment prevented full resolution of the infection. Additionally, the fibrosis associated with the chronic nature of the infection may have hindered complete elimination by the host's immune system and likely contributed to the difficulty in finding organisms. In early infections, polymorphonuclear leucocytes predominate and organisms are generally easy to find. But, as the infection becomes chronic and granulomas form, the number of organisms decreases (Saccente and Woods 2010).

Pathogen factors such as low virulence of the infecting Blastomyces strain or a small dose of inoculum may also explain the slow progression of disease and low number of organisms. Variable strain-dependent virulence resulting in altered disease course and survival times has been reported in mice with pulmonary blastomycosis (Moser and others 1988). Also seen in mice, smaller doses of inoculum resulted in slower disease progression and longer survival times (Williams and Moser 1987).

Other methods for diagnosis were not pursued in the present case but include antigen and antibody testing of urine and serum. The MiraVista Blastomyces antigen test detects a cell wall galactomannan and has 93.5% sensitivity in canine urine and 87% in serum, similar to human studies. There can be antigen cross-reactivity between Blastomyces and other endemic mycoses, such as histoplasmosis. Antibody detection is much less sensitive at 17.4% when performed by agar gel immunodiffusion and 76.1% by enzyme immunoassay (Spector and others 2008).

Itraconazole at a dose of 5 mg/kg once daily is considered by many to be the treatment of choice for canine blastomycosis (Legendre and others 1996, Brömel and Sykes 2005, Ettinger and Feldman 2009). Optimal absorption of itraconazole requires gastric acidity so it should be taken with food (Saccente and Woods 2010). Amphotericin B is as effective as itraconazole but requires parenteral administration and may cause nephrotoxicity (Legendre and others 1996) so is often reserved for initial treatment of life-threatening disease in dogs (Wiebe and Karriker 2005, Crews and others 2008) and people (Saccente and Woods 2010). Similar pharmacokinetics have been found

between innovator-formulated and generic itraconazole; however, compounded itraconazole should not be used due to low absorption and bioavailability (Mawby and others 2014). Additional treatment options, attractive mainly due to their decreased cost, include fluconazole and ketoconazole. Fluconazole treatment has been effective in many cases but may result in a higher mortality rate within the first two weeks of treatment and required longer treatment duration as compared with itraconazole (Mazepa and others 2011). The main side effect of itraconazole and fluconazole is hepatotoxicity and occurred in 26% and 17% of dogs, respectively, in the aforementioned study as evidenced by increases in alanine aminotransferase (Mazepa and others 2011). Ketoconazole treatment is effective in less than 50% of cases, has been associated with lower response rates, longer treatment duration and a higher rate of relapse (Ettinger and Feldman 2009). In the present report, treatment was initiated with fluconazole due to cost concerns and the non-life-threatening nature of the patient's disease. However, when new lesions developed during fluconazole treatment, therapy was changed to itraconazole to improve efficacy and in an attempt to shorten the overall duration of treatment.

Treatment duration varies on a case by case basis and is dependent on the severity of disease (Werner and Norton 2011). As many as 24% of dogs with blastomycosis relapse during the first six months after completion of treatment (Wehner and others 2008), so discontinuation must be carefully considered. Treating for longer than 60 days may reduce the rate of recurrence (Legendre and others 1996). In general, treatment with itraconazole or amphotericin B should be continued for a minimum of two to three months or at least one month beyond full resolution of clinical signs (Kerl 2003, Ettinger and Feldman 2009, Mawby and others 2014). However, some have recommended four to six months of itraconazole treatment (Brömel and Sykes 2005) and the median treatment duration for human patients with non-life-threatening blastomycosis receiving itraconazole is 6.2 months (Dismukes and others 1992). A negative urinary antigen concentration could provide further evidence that a cure had been reached (Foy and others 2014). In the present report, the patient was treated first with fluconazole for approximately two weeks and then with two months of itraconazole for a total duration of nearly 80 days. Despite the owner discontinuing treatment without medical advice before physical examination, at the time of this writing, the dog has not relapsed.

The use of glucocorticoids in cases of blastomycosis is not clear-cut. Concurrent administration of topical and systemic glucocorticoids, along with antifungals, has been advocated in ocular blastomycosis (Finn and others 2007). Glucocorticoids may play a role in vision preservation and were not found to affect survival rate. In a 2008 study on pulmonary blastomycosis, the authors were unable to demonstrate any specific effects associated with corticosteroid use before diagnosis. Corticosteroid-treated dogs did not have worsening of their lobar index (a measurement used to quantify the severity of pulmonary disease) as compared with non-corticosteroid-treated dogs (Crews and others 2008). In cases of severe pulmonary blastomycosis, concurrent steroid with antifungal treatment may avert life-threatening respiratory failure by reducing the host inflammatory response to the dying organisms (Greene 2013). In the present case, steroid treatment, albeit without antifungal treatment, resulted in partial improvement rather than leading to fulminant disease. Along with the host and pathogen factors discussed above, the authors suspect the noted partial improvement was related to reduced cutaneous inflammation. It is important to note that the authors severely caution the use of steroid treatment in dogs with infectious diseases, as this may result in dissemination and worsening of infection through impaired cell-mediated immunity (Kerl 2003). However, further studies on the role of steroids in the treatment of systemic fungal infections such as blastomycosis are clearly needed.

In summary, this case represents successful treatment of chronic canine blastomycosis utilising fluconazole followed by generic itraconazole. At the time of diagnosis, thoracic radiographs were within normal limits with fungal organisms and associated inflammation limited to the skin. Sparse fungi, despite steroid treatment, hampered diagnosis with only a single Blastomyces yeast identified on tape impression cytology and no organisms seen on multiple biopsy specimens even with the use of fungal stains.

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Notes