Proceedings of the
World Small Animal Veterinary Association
Mexico City, Mexico – 2005

Hosted by:

Reprinted in the IVIS website with the permission of the WSAVA
SPOROTRICHOSIS

Introduction

Nodular mycoses are infections of fungal nature which produce small nodules or tumors that tend to present central necrosis (gumma), suppuration and ulceration. Habitually, there is a primary lesion with a subsequent process of nodular lymphangitis. At times, these remain as localized lesions without the satellite cutaneolymphatic form. Among the nodular or ulcerous-nodular mycoses one may include sporotrichosis.

Conceptually it is a human and animal subcutaneous mycosis with zoonotic characteristics (sapro and/or anthropozoonosis) with variable evolution caused by the saprophyte fungus (Division Ascomycota, subclass Euascomycetes, order Ophiostomatales, family Ophiostomataceae, genus Sporothrix sp). In nature, it is typical of tropical and semitropical regions. The fungus (S. schenckii) is monospecific and dimorphic. It lives as a saprophyte in vegetables (soil, organic wastes). It’s been isolated from tree bark, shaganum, moss and conifer seedlings, which probably justify its apparition in gardeners, farmers, animal trainers, florists, seedling handlers and miners.

Given animal habits, especially those of felines in the sense of digging holes and/or covering wastes with earth or sand, or of sharpening claws in tree trunks, it’s perfectly feasible that these animals carry the agent in their claws, even as healthy hosts, which enables them to infect other animals or humans. Other than the cat, the armadillo (Dasypus novemcinctus) is an animal in constant contact with the soil, from which it digs its holes and galleries, being thus incriminated for the transmission of sporotrichosis to humans, as described in Uruguay and Brazil.

In tropical countries as Brazil, among so many others in South America, Asia and Africa, records of human and animal sporotrichosis are extremely common. In Brazil there have been cases diagnosed in mules, donkeys, chimpanzees, bovines, rats dogs and cats. In the case of feline sporotrichosis, the greatest collection of described cases until 1997 was the work that gathered eight cases in the state of Sao Paulo, Brazil.

Recently, in the southeast region of Brazil, in Rio de Janeiro, sporotrichosis has manifested itself in an epizootic form. In the period ranging from July 1998 to December 2001, 347 cases of feline sporotrichosis were diagnosed through the isolation of the agent. A paper dating from 1955 published by Brazilian physician was the first to mention the possibility of feline sporotrichosis transmission to humans. International literature contains other works regarding transmission.

Sporotrichosis is much more frequent in cats than in dogs. In São Paulo, the dog:cat diagnosis rate is 1:30. Historically, the Hospital Veterinário of the Universidade de São Paulo, Brazil, diagnoses 1.5 cases/year.

Clinical Findings

The disease manifests itself in the cutaneous or extra-cutaneous form. Within the cutaneous manifestation, one may note the fixed cutaneous (felines, canines), cutaneolymphatic (canines, equines) and disseminated (felines) forms. Amid the immense number case histories of feline sporotrichosis in Brazil, the most common extra-cutaneous manifestation involves the respiratory system, as observed in 44.4% of cases, where the patient presents dyspnea and sneezing. Rarely one may observe bone-involvement in dogs and cats.

Felines

Affects housed and free-roaming felines, especially males, with the mean age of 2 to 3 years, usually...
Infection usually takes place through fights (71%), contact with infected animals (22.3%) or iatrogenic transmission (5.6%) 30.

Cutaneous lesions consist of crusts over smooth nodules, gummas, draining fistulae, ulcers and vegetation ulcers. They are located in the head (56.8%), especially in the nasal planum (28%), ears (21.6%) and on thoracic limbs (13.8%). They may involve the mucosae (conjunctival, nasal, oral or genital) in about 35% of cats 30.

Even in advanced situations, organic conditions remain unaltered in 70% of the cases. There are reports of 65-week-old asymptomatic infections.

Except for an evident species predisposition, a relative predisposition related to virally immunosuppressed animals is not that frequent. In Rio de Janeiro, cats infected with FIV, FeLV and FIV-FeLV corresponded respectively to 19.7%, 1.4% and 0.7% of sporotrichosis-positive cats 30. Through laboratory tests one may verify the occurrence of anemia, neutrophilic leukocytosis, gammopathies, and hipoalbuminemia. There are no other serological alterations (ALT, AST, BUN and creatinine).

**Figure 1 – Frequency (percentage of cats affected) of serum biochemical abnormalities in 97 cats with sporotrichosis. Arrows indicate increased or decreased values. ALT = Alanine aminotransferase. AST = Aspartate transaminase.**

L1 – Cats with skin lesions at one site, L2 – Cats with skin lesions at 2 sites, L3 – Cats with skin lesions at 3 or more sites30.

**Canines**

Generally, canine sporotrichosis involves only the cutaneous, fixed-cutaneous or cutaneolymphatic forms. Lesions consist of firm, multiple nodules with possible central necrosis. At times, they evolve to form fistulated, exsudative verrucae or warts. Usually there is no pruritus or pain involved. In the cutaneolymphatic form, nodules progress from the initial infection site which is typically in one of the limbs, ascending through the lymphatics, gradually originating secondary nodules, generating the aspect of a “rosary.” In this form there is evident lymphadenomegaly. Because of the small occurrence rate, one is unable to epidemiologically characterize canine sporotrichosis 11, 9.

**Diagnosis**

In order to establish diagnosis, one must bear in mind the real possibility of its occurrence. In humans, differential diagnosis includes leishmaniasis, chromomycosis and tuberculosis. In Brazilian veterinary dermatology, the golden rule for the diagnosis of ulcerated nodular lesions is to seek to differentiate a potential case of sporotrichosis from neoplasms, cryptococcosis or mycobacterial infections.

Diagnosis is based on data collected in identification, anamnesis, dermatological exams and laboratory tests “intra vitam” and “post mortem.”

Cytologic examination (Gram, Wright, Giemsa, fluorescent antibody test) allow for demonstration of the agent, present in the feline under great number of ways, from the material collected from wounds. One may and should perform mycological culture with material collected from lesion fragments or with blood clots (agar Sabouraud, agar BHI, Fava Neto medium) at 25 to 37° C. Subsequently, microcultivation (25°C) should be made for characterization of the micromorphological aspect of the fungus (conidiophores, with elliptical conidia in the shape of a daisy or chrysanthemum). Though rarely used, peritoneal or testicular inoculation of rats or hamsters may be performed.
In veterinary medicine, intradermal reaction with sporotrichin is uncommonly used. In human medicine, a negative result in such test rules out the diagnosis of sporotrichosis. Serological assays that may be used include: complement fixation, agglutination, immunodiffusion, immunofluorescence and ELISA. Recently the validity of immunohistochemistry using polyclonal antibodies against Calmette-Guerrin bacilli in fragment biopsies has been emphasized.

In epidemiological studies of infected asymptomatic and ill felines in Brazil, the agent has been isolated from claws (16.5 to 39.5% of the animals), airways (66%) and oral cavities (42% to 49%) of cats.

Intra vitam histopathological exam from cutaneous lesion biopsies stained by hematoxylin-eosin (HE), Periodic-Acid Schiff (PAS) or silver (Gomori or Grocott), allow for the verification of the nodular or diffuse, suppurative or granulomatous dermatosis. Felines present granulomatous formations in 12% of the exams. There seems to be an inversely-proportional correlation between the presence of granulomas and the histological detection of the agent. Asteroid bodies are rarely shown in cats. Agent may be detected in up to 62% of the histopathological exams. Therefore, by adding up facts such as the lack of asteroid bodies, the low granuloma occurrence and the plethora of Sporothrix, one is able to substantiate the high feline susceptibility to the disease.

Cryptococcosis

Cryptococcosis, also known as European blastomycosis or torulosis, is fundamentally an opportunistic fungal infection to humans, infecting mostly immunosupressed patients (because of infectious as well as iatrogenic causes), and individuals suffering from systemic diseases (Lupus erythematosus and lymphomas.) Among animals, it has been described in birds, bovines, equines, savage felines (leopards), primates, canines and felines. The last pay major tribute to the disease in all latitudes. In Brazil, in the Hospital Veterinário o Universidade de São Paulo, diagnosis is of 1.6 cases/year during the last 12 years, with the feline:canine proportion of 18:1.

Contrary to sporotrichosis, it is not considered a sapro or anthropozoonosis.

In 1895, Francesco Sanfelice published, in a periodical at the University of Cagliari (Italy), the first isolation of the yeast agent, from a fruit juice, calling it Saccharomyces neoformans.

Today, included in the genus Cryptoccus, two of its species are incriminated as causal agents of the disease. In the 5th International Conference of Cryptococcus and Cryptococcosis, the present day nomenclature was proposed: C. neoformans and C. gattii, which substituted the classical species C. neoformans, with two varieties: neoformans and gattii. The complex C. neoformans, which incorporated the two species, was characterized for growing in a temperature of 37°C, differing from the other species of its genus, losing, nevertheless its pathogenicity in temperatures above 39°C.

Characteristically, it produces the capsule constituted by polysaccharides, xylose, mannose, glicuronic acid, sulfur, lactase and phospholipase polymers. Polysaccharides and enzymes have fundamental importance in the virulence of the yeast, protecting it from dissection and phagocytes. Both species of this ascomycete are dimorphic. They transform themselves under special laboratory conditions into the filamentous form (Filobasidiella spp). The importance of the perfect state is that their spores represent the infecting propaguli which yield the disease in mammals, after its deposition in the respiratory tract. Antigenic capsular differences allow for the identification of five serotypes: A, B, C, D and AD.

Both species differ genetically, biochemically and epidemiologically. C. neoformans has a worldwide distribution and C. gattii is restricted to the tropical and subtropical climates. C. neoformans, with basis in serotyping, incorporates the varieties grubii and neoformans and is associated to human immunosupression. Var. grubii is very common in animals from all over the world, and particularly in Brazilian dogs and cats. Var. gattii is important in Australasia (Australia, Papua, New Guinea), Southeast Asia and Central Africa. Eucalyptus flowers are natural reservoirs of the latter. This tree, native from Australia, was exported to Brazil, Mexico, Africa, Asia and USA (Hawaii and California). In Brazil, it has also been isolated from oiti (Moquilea tomentosa), Cassia (Cassia grandis) and fig tree (Ficus microcarpus) fedes.

Var. neoformans does not have a determined environmental niche. It is historically associated to pigeon (Columba livia), koala (Phascolarctos cinerus) and other birds’ (in Brazil: Belgian canary – Serinus canarius, canário-da-terra – Sicalis flaveola, galo-campina – Paroaria dominicana, periquite – Melopotittacus undulatus) feces. (rich in nitrogen compounds as creatinine which provide alkaline, hyperosmolar media, that, in turn, favor its growth). It may survive up to two years in pigeon feces if protected from dehydration and sunlight.

There are reports of coexistence of both species in tree hollows and on the ground.

All Brazilian reports of canine and feline cryptococcosis involve the agent C. neoformans serotype AD. C.
C. neoformans is responsible for cases in Australia and Spain, involving felines, canines, ovines, equines, mustelides and marsupials (koalas).

Predisposition and Pathogenesis

As in human medicine, veterinary medicine has incessantly sought predisposing factors to the installation of infection. In humans, cryptococcal meningitis is related to viral infection (HIV) and sarcoidosis. Based on speculation, feline cryptococcosis could be associated to FIV/FeLV infection, whilst, in canines, predisposition could be related to ehrlichiosis. Nevertheless, Australian, North American and Brazilian studies don’t confirm such suspicion, since FIV and FeLV prevalence among cats with cryptococcosis and those of the normal feline population seem to be alike. In Brazil, predisposing factor relative to feline viral infections is of small incidence (10% of cases).

In Brazil susceptibility of felines is clearly greater than that of canines. It is more frequent in cats over 4 years of age (62%), with the mean age of 63 months, in males (75%), of selected breeds, especially in the Siamese (60%). In this country there are rare reports of canine cryptococcosis. In the USA and Australia, dogs with the mean age of up to four years of the Doberman, Great Dane and Cocker spaniel breeds are the most affected.

The exact means through which the infection occurs is still under debate. It is most likely to take place through the respiratory system, via inhalation of basidiospores or dehydrated yeast cells since carnivore, marsupial and psittacine birds nasal cavities and paranasal sinuses constitute the primary site of infection. Multifocal cutaneous involvement reflects bone (phalanges), periarticular tissue or hematogenous dissemination from the primary site (cryptococcoma). Such fact is unyielding in ferrets and cats, when percutaneous penetration occurs. There are cases when infection disseminates through the cribiform plate to the bulbs and olfactory tracts, leading to meningoencephalitis, which is very rare in Latin America. Anatomical proximity to the optic nerve leads to concomitant optical neuritis and secondary retinitis. Caudal nasal cavity involvement with polipous lesions causes the occlusion of the choanae with consequent respiratory symptoms. At times, dissemination to the mid-ear through the Eustachian tube may take place. There is no doubt that cryptococcosis pathogenicity involves a mechanism of evasion from the immune defenses, and is aggravated by the overwhelming use of immunosuppressant drugs.

Clinical Findings

The following table gathers symptoms and lesions related to canines and felines with cryptococcosis:

Table 1: Clinical manifestations and lesions of canine and feline cryptococcosis

<table>
<thead>
<tr>
<th>System</th>
<th>Symptoms/ Signs/ Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory (upper)</td>
<td>Sneeze, nasal discharge, epistaxis, nasal deformities and nasal occlusion, osteolysis, increased respiratory noise, dyspnea, buccal respiration, chronic cough, pleural effusion</td>
</tr>
<tr>
<td>Cutaneous*</td>
<td>Papules, nodules, ulcers, abscesses, mucocutaneous deformities**</td>
</tr>
<tr>
<td>Skeletal</td>
<td>Lameness, onychomadesia, osteonecrosis of phalanges, digital edema</td>
</tr>
<tr>
<td>Nervous</td>
<td>Depression, behavioral changes, seizures paresis, ataxia, blindness, anosmia, head tilt, head pressing</td>
</tr>
<tr>
<td>Optic</td>
<td>Blindness, absent pupillary light reflex, chorioretinitis, retinal detachment</td>
</tr>
<tr>
<td>Other</td>
<td>Lymphadenomegaly, loss of appetite</td>
</tr>
</tbody>
</table>

* present in 20% of canines and 40% of felines

** “Clown nose,” “eagle nose,” “Ottoman nose”

Diagnosis

For the diagnosis of both diseases there are no major difficulties. Symptomatic and lesional manifestations are relatively characteristic. However, the differential diagnosis with other infectious diseases and neoplasms should be done.

Table 2: Cryptococcosis and sporotrichosis differential diagnosis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
</table>
Other than identification (species, breed, age), anamnesis (symptoms, contacting animals, location, management, primary diseases, medications used), physical exam, dermatological exam, laboratory tests (x-rays, tomography, direct mycological exam, culture, histopathology and serology). Routine subsidiary exams that generate correct diagnosis are, in sporotrichosis: histopathology (HE, PAS, Gomori, Grocott) and culture (Sabouraud with cycloheximide, BHI, Fava Neto medium). In cryptococcosis, one is able to witness the agent through imprints of secretions, lymph node aspirates, lavages (nasal, bronchoalveolar) and CSF, stained by New Methylene Blue, Gram and India stains, in 75% of cases. Culture of aspirates, exudates, CSF and tissue samples in Sabouraud agar without cycloheximide, propitiates rapid growth. Histopathology (PAS, Gomori, Grocott, Masson-Fontana) is the procedure used to attain definitive etiological diagnosis. Mayer’s mucicarmine is the preferred staining technique. Serological testing is indicated in cryptococcosis for all its serotypes, where the capsular antigen is detected, through the latex agglutination procedure.

**Sporotrichosis Therapy**

The common protocol for treating sporotrichosis uses “per os” halogenated drugs, like sodium or potassium iodide, 20% super saturated solution. French researchers proposed iodine to treat human and animal sporotrichosis in the 19th century, and even nowadays, it is extremely effective in human, canine and equine patients. Doses of 40 mg/kg or 10-20 mg/kg once a day, “per os” are indicated to dogs and cats, respectively, always with food or fatty liquid (cream or whole milk). The metallic taste is extremely unpleasant, so nausea or emesis may be observed. Iodism is not rare in cats. Although the traditional reference about its efficacy in feline sporotrichosis, this is not true in Brazil. Up to 1993, all cats were unsuccessfully treated with NaI or KI at Hospital Veterinário de Universidade de São Paulo. Over the last eleven years, itraconazole has been successfully used (10 mg/kg, “per os”, q24h), alone or associated with fluocytosine (40-60 mg/kg, “per os”, q24h). The only disadvantages of this protocol is the necessary time to get cure (until 7 months of treatment), and its cost.

In some cases terbinafine has been recommended although there is no recommended standard doses. 

**Cryptococcosis Therapy**

The common protocol is the same recommended for feline sporotrichosis, that is, the single use of itraconazole or in association with fluocytosine (5-fluorocytosine), in the same referred doses. A long period of treatment (6-12 months) guarantees the success, particularly in feline and canine neurophtalmopaties.

Recently, cases of toxic epidermal necrolysis associated with therapy regimens using fluocytosine in association with amphotericin B or triazoles were described. Circumstantial evidences strongly suggest that is fluocytosine component of therapy which triggered this response. This side effect has not been observed in several cases treated with this drugs association in São Paulo, as opposed to what is referred in literature there was no difference in response to triazol-pyrimidine association among FIV or FeLV seropositive and seronegative cats.

Alternatively, ketoconazole (dog: 5-15 mg/kg, q12h, PO; cat: 5-10 mg/kg, q12h, PO); fluconazole (50 mg/cat/day for nasal and dermal cryptococcosis, and 2,5 –10 mg/kg/day for cryptococcal meningitis); amphotericin-B lipid complex – ABLC - (dog: 2-3 mg/kg, IV, 3 days/week, for 9-12 treatments; cat: 1 mg/kg, IV, 3 days/week for a total of 12 treatments) are recommended.

In all cases cryptococcosis in cats as well in dogs (rare in Brazil), the use of itraconazole (alone or in association with fluocytosine) was effective and with no side effects.

**BIBLIOGRAPHY**


Contact with the author: larsderm@usp.br

"HE staining of histological cuts reveal the yeast cell surrounded by radiated eosinophilic material constituted by the complex resulting from antigen-antibody deposition."