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David C. Twedt Jr.
Iowa State University

David L. Graham
Iowa State University

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Systemic Mycoses in Small Animals

by

David C. Twedt Jr.*
and
David L. Graham B.S., D.V.M.†

INTRODUCTION

There are few organic substrates in man's environment which are free from fungi. Some of these saprophytic fungi can adapt to the parasitism of man and animals. The fungi which can cause systemic mycoses in animals are normally saprophytes which grow in soil which is enriched by humus, decaying vegetation, or nitrogenous waste such as fecal material of animals and birds. They are capable of growing indefinitely on these substrates with the proper environmental conditions with no need of a parasitic cycle in animals. When an animal is infected, the reproductive cycle in most instances is terminated. The transmission to animals is primarily by means of spores which are inhaled from an exogenous source and cause involvement of the respiratory system. The organism though, can enter by ingestion or skin puncture. After the initial entry, subsequent secondary spread and involvement of other systems may result.

In recent years there has been an increase in the clinical diagnosis of systemic mycotic infections in both man and animals. There is probably not a significant rise in the number of systemic mycoses, but during recent years there has been an increased awareness of mycoses on the part of clinicians and pathologists, wider availability and use of laboratory diagnostic techniques, and improved staining techniques which have increased the diagnosis of systemic mycoses.

It is felt that even with better diagnostic techniques, the veterinarian often tends to overlook the possibility of a mycotic disease in his differential diagnosis. Systemic mycoses are not as rare in small animals as some may believe. This paper will describe the most frequent systemic mycotic diseases encountered in a small animal practice. The diseases of medical importance are histoplasmosis, blastomycosis, coccidioidomycosis, cryptococcosis, actinomycosis, and nocardiosis.

The geographical distribution of the systemic mycotic diseases common to small animals is varied and not completely understood. There are certain environmental conditions which are required for the growth and proliferation of the organisms. With the proper ecologic associations, the organisms proliferate and local endemic areas occur. Though there are areas of higher incidence, with the increase in travel by members of our society, it is possible to see any systemic mycotic disease in any practice. The following will be a description of each.

HISTOPLASMOSIS

Histoplasmosis, or Darling's disease, is an asymptomatic acute, subacute, or chronic infection which is caused by Histoplasma capsulatum. It is the most com-
mon systemic mycosis in the dog in North America." It is rare in the cat.

*Histoplasma capsulatum* is a dimorphic fungus which grows in nature as a mold with slender mycelium. It is found in soil or excreta of bats and birds and proliferates under proper climatic conditions. Though there are local areas of high concentration, the geographical distribution is the Mississippi, Ohio, and St. Lawrence river valleys. Histoplasma incidence is also high along the Appalachian mountains and areas of North Carolina. In these areas, isolations of the organism have been made in soils of a high per cent of organic material. These soils are usually contaminated with excreta of starlings, pigeons, chickens, or bats. Birds are apparently immune to histoplasmosis because of their high body temperature, but their excreta provides environmental conditions which will support fungi.

The transmission to animals occurs when spores are released into the air and are inhaled by the animal. The spores may also be ingested or enter by skin contact. Once the spores enter the animal, the fungus grows as a yeast form which has a marked predilection for the reticuloendothelial system causing a granulomatous disease. This yeast is a small budding fungus 2 to 3 microns in size found intracellularly in phagocytes.

Clinically, histoplasmosis is found in dogs between four months and six years of age. Frequently the condition is asymptomatic and causes no problem. One report indicates that 40 to 50 per cent of the dogs in an endemic area had exposure to this fungus. Usually these animals have arrested the lesion and the fungus is walled off. The disease then causes no clinical signs, but is resolved spontaneously and frequently heals as calcified nodules in the lungs.

Histoplasmosis should be considered in a differential diagnosis of all animals with a chronic cough or persistent diarrhea. The disease is then in an active condition and is frequently disseminated to various parts of the body. From a clinical standpoint the disease can be divided into three main forms; a pulmonary form, an intestinal form, and a cutaneous form.

The pulmonary form of histoplasmosis is the most commonly seen. When the spores enter the respiratory system, there is an invasion of the reticuloendothelial system by the yeast form of *Histoplasma capsulatum*. The yeast form usually is confined to the bronchial and mediastinal lymph nodes, though it can be distributed throughout the lung as miliary nodules. The histiocytes containing *Histoplasma capsulatum* multiply by great numbers, thereby crowding out and replacing normal tissues.

The animal with the acute pulmonary form shows an elevated temperature, dyspnea, and rapid emaciation. The chronic form is represented by a non-productive cough, vomition, dyspnea associated with enlarged bronchial lymph nodes, and intermittent fever. By means of radiograph, granulomatous lesions can be seen throughout the lung parenchyma. If the primary lung lesions do not heal spontaneously, dissemination by means of the blood stream can occur with involvement of the reticuloendothelial systems of various organs. A generalized lymphadenopathy then occurs.

The intestinal form can occur by the spread of the organism from the pulmonary form, or through ingestion of the fungus. The lesions are confined to the mucous membranes and the mesenteric lymph nodes. The clinical signs are characterized by a chronic, often bloody diarrhea, enlargement of mesenteric lymph nodes on palpation, secondary anemia, and emaciation.

The skin form can be caused either by dissemination or by local exogenous contact. If it is an active dissemination there are usually other clinical signs present and the prognosis is poor. With a local skin infection, the prognosis and treatment are favorable. The lesions are that of an ulcerative dermatitis and are frequently seen between the digits and around the feet and legs.

**BLASTOMYCOSIS**

North American Blastomycosis, or Gil-
Christ's disease, is a common mycosis of dogs in the United States. Blastomycosis is usually a chronic or systemic granulomatous disease which originates primarily as a respiratory tract infection.\(^{2}\) Dissemination to skin, abdominal viscera, and bone can occur. The disease is caused by *Blastomyces dermatitidis* which is a dimorphic fungus. The saprophytic form grows in the soil, but the type of soil or environmental conditions required by this organism are not known as they are for histoplasmosis. The geographical distribution of blastomycosis is almost throughout the United States with areas of higher concentration along the Ohio river, Missouri river, Upper Mississippi river valley, and in the south-eastern United States.\(^{1}\)

The route of infection is primarily by inhalation and invasion of the respiratory mucosa. The bronchi, mediastinum and lung parenchyma are involved. The fungus is a large (8 to 15 microns) budding yeast. The characteristic tissue response is a combination of suppuration and epithelioid cell granulomatous reaction with giant cells.\(^{1}\)

Dissemination of blastomycosis tends to be more frequent than with histoplasmosis.\(^{3}\) The formation of nodules on the skin changing to abscesses and draining fistular tracts is fairly common. Skeletal lesions may occur via the hematogenous route or by extension from subcutaneous tissue. Ocular lesions have been reported with the disseminated form.\(^{1}\)

An animal presented with blastomycosis is in a chronic wasting condition.\(^{4}\) They usually show a persistent cough and may have skeletal lesions or draining fistulas. The transmission from animals to man is rare, but there are reported cases of blastomycosis in humans due to dogs with skin involvement.\(^{4}\)

### COCCIDIOIDOMYCOSIS

The causative agent for coccidiodomycosis is *Coccidioides immitis*. This organism is very limited in distribution. In the United States it is found only in the lower elevation desert areas of the Southwest, where it proliferates in the soil. Consequently it is often called "San Joaquin Valley Fever" or "Rodent Fever." This fungus is dimorphic and is in the mold form in soil. This saprophytic mold liberates arthrospores which gain entry into tissues of susceptible animals. An inhaled arthrospore of *Coccidioides immitis* enlarges and becomes spherical within a few days. It is then called a spherule. As it attains maturity, it produces endospores. Which can then be released from the spherule and spread to other parts of the body. The spherule causes a giant cell granulomatous reaction in the host. After release, the endospores cause a pyogenic reaction with surrounding neutrophils.\(^{5}\)

The most common site of infection is the lung, but cutaneous infections may result. The disease usually results in a benign, self limiting condition of the respiratory tract. Less common are chronic fulminating granulomatous reactions. In disseminated cases, the disease extends to other visceral organs, bones, joints, and to the skin. The boxer dog seems the most susceptible to the disseminated disease.\(^{6}\)

In the primary disease condition with respiratory exposure, few clinical signs are seen. Dogs may show a slight fever, variable anorexia, and listlessness. They may develop a slight cough and often the illness is not recognized. Research has shown that 18.5 to 47 per cent of the infected dogs in an endemic area remain clinically asymptomatic.\(^{7}\) These mild conditions may regress for a time, but then eventually they can disseminate.

The dissemination of coccidiodomycosis is characterized by increased respiratory involvement, although coughing is not always associated with this; involvement of other organs of the body such as the liver, kidney, skin, and long bones occurs frequently. Loss of weight, ascites, and sometimes lameness are seen. The condition is usually chronic, lasting for months and frequently years.\(^{8}\)
**CRYPTOCOCCOSIS**

Cryptococcis is a systemic mycosis that is most frequently seen in cats 4 years of age and older. Cryptococcus neoformans, the causative agent, is a monophasic, nonmycelial yeast. It ranges from 5 to 18 microns in size and is surrounded by a thick capsule of 10 microns.

Cryptococcis, Torulosis, or European Blastomycosis is found worldwide and there seems to be no breed or sex predilection for the disease. The organism is a saprophyte in the soil and only an accidental pathogen of animals. The fungi usually enter by inhalation and the primary source has been associated with dust and debris of pigeon droppings. When the organism enters tissue, a thick capsule develops. The disease originates in the respiratory tract and can cause nasal, nasal pharyngeal, or pulmonary granulomas. This is often characterized by chronic nasal or ocular discharges. Dyspnea is often present. Cryptococcus can disseminate and has a predilection for central nervous system (CNS) tissue and can localize in the skin. Cryptococci should be considered in cases which have CNS involvement. The primary clinical manifestation may be similar to those of tumors, CNS abscesses, and meningitis due to other organisms. These signs usually develop after the appearance of skin lesions or pneumonia. The disease is never acute and usually lasts for months to years.

The lesions in the CNS are distinct and differ from other CNS granulomas. The presence of a mucoid or gelatinous material in or on nervous tissue strongly suggests cryptococcis.

**NOCARDIOSIS**

Nocardia asteroides is a filamentous fungus found as a common saprophyte of soil and plants in the United States. The portal of entry is probably to a great extent by air-borne means, although wound infections and oral ingestion are other means of entry. The organism then grows as a multiple superficial or deep granulomatous lesion. The superficial lesions are characterized by numerous draining sinuses opening to the skin's surface.

The invasion of the respiratory tract results in pneumonia. Very frequently a pleuritis develops which is purulent to hemorrhagic. With this proliferative response, pleural effusion in the form of a reddish brown exudate develops. The animal shows a nonproductive cough and dyspnea. There is also a notable predilection for the CNS. A severe encephalitis results and causes clinical signs similar to canine distemper. Concurrent nocardiosis and distemper have been reported. Dissemination to the gastrointestinal tract, visceral organs, and bone occur.

A very frequent means of entry is through the skin resulting in tumorous masses found usually on the extremities. These growths are called mycetomas and are filled with small sinus tracts draining a thin serosanguinous discharge which may contain small yellow white granules.

**ACTINOMYCOSIS**

Actinomycosis is a chronic suppurative disease characterized by contact spread to adjacent tissues. It frequently forms sinus tracts which drain suppurative lesions. Present in the exudate are firm lobulated colonies of fungi which are white to yellow in color and called “sulfur granules.”

*Actinomyces israelii* is a higher form of fungi related closely to bacteria. It is usually a normal saprophyte of the oral cavity in animals and consequently many infections are probably endogenous in origin. For example, the organism may enter through dental alveoli and result in abscesses of the cervical region and draining lesions about the face and neck.

In most cases the lesions of actinomycosis and nocardiosis are indistinguishable. The pleural lesions are very similar. The clinical signs depend largely on the means of entry into the host by the organism. Actinomycosis can cause involvement of the nasal cavity with destruction of the turbinates and sinuses. It can cause pneumonia and granulomatous lesions in the lungs. When there is entry through skin and development of mycetomas, the
organism may invade deeper and cause osteomyelitis of adjacent bone."

**DIAGNOSIS**

With recent advances in veterinary medicine and the availability of modern laboratory facilities, the diagnosis of systemic mycoses has become possible. Because of the wide variety of clinical signs that can be seen with each disease, the clinical syndrome can only add suggestive evidence of a particular systemic mycotic disease. Because of our highly motile society, the veterinarian cannot rule out a condition simply because he is not in an endemic area. A thorough history is often contributory to an accurate diagnosis.

Radiography is very useful as an aid to the diagnosis of a granulomatous fungal lesion in the lungs. The main radiographic sign is the presence of rounded masses with indistinct or fuzzy borders. It is often denoted as the "cotton ball" appearance. The location is mainly around the hilar areas and frequently, enlarged lymph nodes can be detected. The granulomas may disappear or become calcified in an old condition.

Skin tests for dermal hypersensitivity can be performed on animals suspected of exposure. The results of such tests are often not rewarding. A positive test reflects exposure to the organism and not that the infection is necessarily active or recent. In fact animals with an active disseminated case will probably be negative when the skin test is performed. There is also very frequently cross reactions with histoplasmosis, blastomycosis, and coccidiodomycosis. A skin test kit for mycotic fungi can be obtained from Hollister-Stein Laboratories, Afedon, Pa.

More reliable tests are the precipitin tests and complement fixation tests. These tests require that a serum sample be taken early in the course of the disease and a second sample later in the course. A positive test is said to reflect an extensive dissemination of the disease. The test results may be negative or indefinite during the early stages of the course. Many well equipped laboratories can handle these tests. Some authorities feel that the complement fixation test has been disappointing when used to diagnose cases in dogs. In recent years a fluorescent antibody test has been used, but the results have not been consistent. Though the above methods may aid in the support of a diagnosis, a positive diagnosis can only be made by demonstrating the organism in tissues or exudates, or by means of growth and isolation of the organism.

Impression smears often prove to be very useful to the veterinarian and are relatively easy to perform. Smears of exudates or impressions of tissues can be made with little effort and can possibly confirm a diagnosis. Gram-stained smears are useful in the diagnosis of actinomycosis. Gram and modified acid-fast stains are useful for nocardiosis. An air dried methyl alcohol-fixed and Giemsa-stained film of pus, bone marrow, or tracheal exudate may demonstrate *Histoplasma capsulatum*. Cryptococcosis can be seen with its large capsule in the usual Romanovsky stains.

The examination of sections of tissues obtained by biopsy or necropsy is important and one of the few definitive means of reaching a diagnosis. Standard histological methods are used, but it is important to use special stains such as periodic acid-Schiff, Gridley, mucicarmine, and methenamine silver stains. They are selective for fungi and permit their demonstration, which because of small size of scarcity may be missed.

If a fungus is too scarce in an exudate to be found or if it is not sufficiently distinctive for specific identification, it is necessary to isolate the fungus in culture. The usual medium is Sabourauds agar. The organism is grown around 25°C and should be left to grow for one month before a culture can be discarded as negative. The culture is then examined microscopically for the proper morphology.

**TREATMENT**

Although fungal infections range from subclinical conditions to a progressive and
The early stages of actinomycosis and nocardiosis respond well to the combination of penicillin and Sulfadiazine. The therapy involves oral administration daily for two to four months at a dosage of 2 to 3 grams of Sulfadiazine. Penicillin is given twice daily intramuscularly at a dosage of 600,000 units for the first two weeks.

The transmission of any of these mycotic diseases from animal to man is extremely rare, although there are some reported cases. It probably occurs only in cases with draining abscesses which contaminate the premises and even man. Under these circumstances, the public health aspect should be pointed out to the owner and euthanasia considered.

REFERENCES


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