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Review Article

Mycetoma in Animals: A Review of Cases Reported From 1925–2022; Epidemiology and Management Strategies

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Mycetoma is a chronic, granulomatous disease of humans and various domestic animals caused by diverse causative agents. Recently, this mycosis has gained a bad reputation due to the appearance of new endemic areas, recognition of new pathogenic species, changes in epidemiology, and increasing numbers of cases. The etiological agents in eumycetoma seem to differ in humans and animals. For example, *Madurella mycetomatis* is the most common species in humans, but only two cases have been reported in animals. While in animals, the most common agents were *Pseudallescheria boydii.* However, there are few case reports and studies in animals compared to those in humans, especially in endemic areas. Considering the epidemiological importance, taxonomic evolution, and worldwide distribution of these fungi in the last decade, there is interest in identifying the species causing mycetoma in animals in different regions of the world. The present article only highlights the geographic distribution of animal mycetoma in the world, and the development and epidemiology of antifungal treatment in animals will also be discussed.

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Abbreviations

Scedosporium/Pseudallescheria complex, SPC; Itraconazole, ITC; voriconazole, VRC; posaconazole, POS.

Introduction

Fungi are relatively uncommon causes of disease in healthy humans and animals, even though hosts are constantly exposed to infectious agents [1][2]. However, an increasing number of fungal diseases in animals have occurred over the last two decades, originating from opportunistic and pathogenic fungi [2][3][4][5].

From a global perspective, zoonotic infections have been recognized for many centuries and account for the majority of emerging and reemerging infectious diseases worldwide [6]. Naturally, individuals at highest risk for developing zoonotic diseases include those in occupations that expose them to animals or animal products, such as veterinarians and veterinary personnel. A household companion animal also may be implicated as the source of zoonotic infections in humans. However, mycetoma is a disease of humans and various domestic animals caused by diverse causative agents. It was common in gardeners, farmers, or people who had contact with plants and soil of natural environments where the fungus could be present in organic materials. On the other hand, the presence of mycetoma infections in animals distinguishes mycetoma as an occupation-independent

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disease and therefore considered an implantation mycosis caused by species of dematiaceous fungi and actinomycetes that usually affect the skin at the subcutaneous levels.

Furthermore, the recognition of mycetoma as a neglected disease with a relevant socioeconomic impact on the country's development obstructs the identification of risk factors and groups. In this context, this systematic review addresses advances in the knowledge of zoonotic mycetoma as a disease caused by environmental fungi and bacteria worldwide and discusses the points that contribute to mycetoma still being considered a neglected disease. The development and epidemiology of antifungal treatment in animals will also be discussed.

Etiology of Mycetoma: Historical Aspects

Mycetoma can be caused by fungi (eumycetoma) or bacteria (actinomycetoma) with similar clinical presentation [7][8][9][10]. Many fungal and bacterial agents of human mycetoma have been reported in the literature, belonging to an array of unrelated genera [11]. Actinomycetoma can be caused by aerobic agents that enter the human body through trauma. The most important agents are *Streptomyces somaliensis, Actinomadura madurae; Actinomadura pelletieri, Nocardia (N. brasiliensis; N. asteroides; N. otitidis-caviarum; N. transvalensis)* [7][8][9].

Approximately 50% of mycetomas are eumycetomas. The melanized species causing black-grain eumycetoma worldwide belong to at least two different orders of *ascomycetes:* the *Sordariales*, the *Pleosporales*, and the *Chaetothyriales* [11] and the most common species are *Madurella mycetomatis* (70% of cases), (as well as the related *M. pseudomycetomatis, M. fahalii, and M. Tropicana*). Other causative agents include *Falciformispora senegalensis* and *Trematosphaeria grisea*. Rarely, *Exophiala jeanselmei, Medicopsis romeroi,, Phialophora verrucosa*, and *Chaetomium atrobrunneum* can cause eumycetoma [12].

Mycetomas in domestic animals, including dogs, cats, and horses, have been reported mostly in North America, southern regions of the United States, South Africa, the UK, and Australia, but in much fewer numbers [13][14][15][16][17] , thus suggesting that mycetoma, in animals as in humans, is primarily a subtropical or tropical disease.

The etiological agents in eumycetoma seem to differ in humans and animals. For example, *Madurella mycetomatisa* is the most common species in humans, but only two cases have been reported in animals. While in animals, the most common agents were *Pseudallescheria boydii* (Figure 1), similar to human mycetoma in the United States and North America, which is commonly caused by *Pseudallescheria* [15][18] . Followed by *Curvularia geniculata, Curvularia verruculosa* [19][20][21][22][23][24], *Drechslera spicifera* [25] *Bipolaris spicifera, Scedosporium apiospermum, Aspergillus verruculosa* [26], *Aspergillus terreus* [27] *Phialophora oxyspora* [28] and *Madurella mycetomatis* [29].

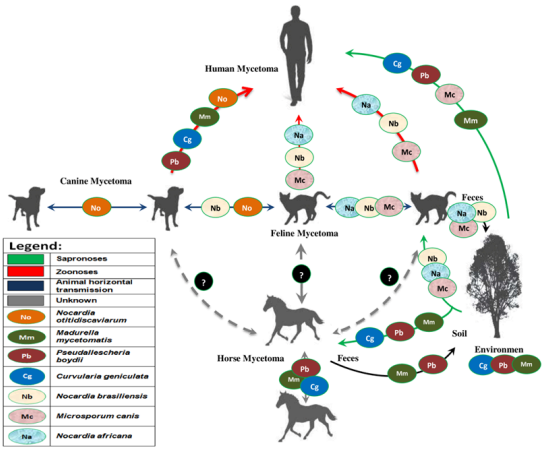

Figure 1. Transmission routes in human and animal mycetoma. The transmissibility between different species of clinical interest is explored based on literature review data. **(A)** *Nocardia otitidiscaviarum and Nocardia brasiliensis* are associated with large epizootics during animal horizontal transmission (blue route). This is not an exclusive host association, since *Nocardia africana* may also infect cats but with lower frequency. Cat-borne mycetoma can be transmitted to humans (zoonoses) via deep scratching and biting (red route). The threat of cross-species pathogen transmission (blue and red routes) poses the risk of a massive epidemic for humans in highly endemic areas. **(B)** In the sapronotic route (classical pathway), the presence of the etiologic agents of mycetoma in nature can lead to an endemic profile, with fluctuation in the number of transmissions. However, the infections remain close to the baseline over time. **(C)** In the alternative route, feline-borne transmission via deep scratching is highly effective during animal horizontal transmission and during zoonotic transmission, placing a larger number of individuals at risk of acquiring mycetoma.

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On the other hand, actinomycetoma reports have been relatively rare. Actinomycetales are Gram-positive, branching, filamentous bacteria. They grow in anaerobic/microaerophilic (Actinomyces species) or aerobic (Nocardia species, *Dermatophilus congolensis, Streptomyces griseus*) conditions. All genera may be responsible for chronic, suppurative granulomas characterized by abscess formation and marked fibrosis that are frequently unresponsive to routine antimicrobial therapy. Grains that stain intensely blue with hematoxylin occur within the abscesses, and with special bacterial stains, densely packed clusters of fine, branching, filamentous organisms can be seen within the grains. It is important to differentiate actinomycetoma from actinomycosis and nocardiosis.

Actinomycosis is a chronic, suppurative disease caused by a gram-positive, non-acid-fast, branching, filamentous anaerobic organism. The lesion is characterized by the presence of granules, commonly called "sulfur granules," containing the organism. There are two well-established species responsible, namely, *Actinomyces israelii* and *Actinomyces bovis* [30]. The two species are not host-specific, but *Actinomyces israelii* has been found most frequently in humans and *Actinomyces bovis* in domestic animals, particularly cattle. A third species, referred to as *Actinomyces baudeti,*, has been isolated from dogs and cats [31][32]. The sites most frequently affected in humans are cervico-facial, thoracic, and abdominal [33], whereas “lumpy jaw" is the usual syndrome in cattle. In swine, the organism produces mastitis [34], and in horses, it is associated with "poll evil" and "fistulous withers" [35]. In dogs, cutaneous, thoracic, and abdominal forms are most common.

Nocardiosis is an acute, chronic, suppurative, or granulomatous infectious disease [36]. It is Gram-positive, acid-fast, but does not stain with H and E. It is a non-capsulated, non-motile, non-sporulated, and aerobic actinomycete, which consists of thin, delicate, slender, beaded filamentous hyphae of 1μm or less in diameter. The organism occurs in the environment as a saprobe and has been isolated from the soil, water, air, dust, and decaying vegetation [37][38]. Currently, over 50 species of Nocardia have been identified by phenotypic and molecular methods. *Nocardia asteroides* complex is the principal species, which is implicated in various clinical disorders of humans and animals, including birds [39]. The *Nocardia asteroides* complex has been recognized as type I, II, III, IV, and V. Type III is called *Nocardia nova,* and type V as *Nocardia Farcinia* [40]. Recently, *Nocardia cyriacigeorgica* was differentiated from *Nocardia. asteroides*, and is now considered an emerging pathogen in the United States [41]. Hamid and co-workers isolated *Nocardia africana*, a new pathogen, from patients with pulmonary infections [42].

The recorded history of nocardiosis goes back to the year 1888 when Edmond Nocard first described a pathogenic aerobic actinomycete in cattle with bovine farcy on the Island of Guadeloupe, West Indies [43]. However, the first human case of the disease was reported in a 52-year-old glassblower in 1890 by Eppinger [44]. Pal is credited with elucidating for the first time the etiologic role of *Nocardia asteroides* in a corneal ulcer of cattle from India [45].

On the other hand, *Nocardia asteroides* does not form granules in tissues; however, other species such as *Nocardia caviae*, *Nocardia mexicana*, and *Nocardia brasiliensis* are characterized by the presence of granules [46][47][48][49][50].

Cattle and dogs are more affected than other species of animals [36][51]. Bovine mastitis is the most common clinical presentation of nocardiosis among domestic animals [52]. In earlier studies carried out in Brazil, [53], *Nocardia asteroides* and [54] *Nocardia brasiliensis* strains were identified as the most common causative agents of cattle mastitis [55].

The disease in canines is manifested with a variety of clinical presentations. The cutaneous or subcutaneous form of the disease, which, similar to human mycetoma, shows purulent draining sinuses producing tomato soup-like exudates [51][56], is of particular concern. *Nocardia otitidiscaviarum* was isolated from eight cases of cutaneous-subcutaneous lesions and one case of pneumonia in dogs in 2008 in Brazil [57]. Recently, Hattori and co-investigators isolated *Nocardia. africana* from a case of mycetoma in a cat [58]. *Nocardia brasiliensis* is the most frequently recognized agent of mycetoma. Recently, Rodriguez-Nava and others reported *Nocardia mexicana*, a new pathogen from human mycetoma (Figure 1)[48].

Transmission

Mycetoma causative agents generally follow an environmental transmission route via traumatic inoculation of contaminated plant debris or from soils. For over a century, this route has affected specific occupational populations, including agricultural workers and gardeners. On the other hand, the presence

of mycetoma infections in animals distinguishes mycetoma as an occupation-independent disease.

Descriptions of Selected Case Reports of Mycetoma in Animals: Canine Mycetoma

Eumycetomas mainly occur in tropical and subtropical regions, and only 19 cases have been reported in dogs (Table 1). Most of the reports were from the United States [15][18][19][20][23][59][60][61] as early as 1925 by Krishnamurti (cited by Davis & Shorten, 1936) [62]. With one exception, in Turkey [63], sporadic cases were diagnosed in Korea, [64] Australia, [65] India, [66] South Africa, [67] Israel [23] France [68] and Italy [69][70]. The pathogens were diverse, including *Curvularia geniculate* [71], *Curvularia lunata, Scedosporium apiospermum, Aspergillus terreus* [66], *Aspergillus fumigatus, Madurella mycetomatis* [67], *Microsporum canis* [69] *Cladophialophora bantiana* [68][72] and *Madurella pseudomycetomatis* [70].

Host species	Country [Ref.]	Etiology	Diagnosis/Identification	Treatment	Response
Horse	USA [20]	*Drechsleraspiciferum*	Histopathology	NA	NA
	Germany[73]	*Scedosporiumapiospermum*	Histopathology, Culture	Surgery+ iodine,	Cured
	Canada [14]	*Scedosporiumapiospermum*	Histopathology, Culture	Antifungal/surgery	No response
	USA [74]	*Scedosporiumapiospermum*	Culture	Surgery	Cured
	South Africa [13]	*Curvulariageniculata*	Histopathology	NA	NA
	Australia [22]	NA	Histopathology	NA	NA
	Czech Rep. [75]	*Pseudallescheriaboydii*	Histopathology	NA	NA
	South Africa [76]	*Madurellamycetomatis*	Histopathology, Culture	NA	NA
	USA [16]	*Scedosporiumapiospermum*	Histopathology, Immunological	Surgery+ iodine,	Cured
	Argentina [24]	*Curvulariaverruculosa*	Histopathology, Culture	Surgery	Cured
	USA [26]	*Aspergillusversicolor*	Histopathology, Culture	Surgery	Cured
	France[27]	*Aspergillusterreus*	Histopathology, Culture	Potassium iodide 30 mg/kg orally once daily / pergolidemesylate 1 mg orally once daily	Cured
	USA [28]	*Phialophora oxyspora*	Histopathology,, Molecular	Surgery+ iodine,	Cured
	Israel [29]	*Madurellamycetomatis*	Histopathology, Culture, Molecular	debridement and bandaging with an ointment containing triamcinolone, nystatin, neomycin, and gramicidin	Increased
Faline	Japan [77]	*Microsporumcanis*	Histopathology, Culture	Surgery	Recurrent
	UK [78]	*Exophialajeanselmei*	Histopathology, Culture	Surgery	Died
Cattle	Australia [79]	*Drechslerarostrata*	Histopathology, Culture	Penicillin and streptomycin	Increased
Canine	Israel [23]	*Curvularia lunata*	Histopathology, Culture	itraconazole.+Surgery	Died
	USA [71]	*Curvularia geniculate*	Histopathology, Culture	NA	NA
	Australia [65]	*Curvularia geniculata.*	Culture	Surgery+ iodine, trirnethoprim-sulphadiazine. amphotericin B. dimethyl sulphoxide, thiabendazole and nystatin	Cure
	Italy [69]	*Microsporum canis*	Histopathology, Culture immunohistochemistry	itraconazole at the dosage of 10 mg /ml every 24 h,+ surgical excision	Cure

Host species	Country [Ref.]	Etiology	Diagnosis/Identification	Treatment	Response
	Italy [69]	*Aspergillus fumigatus*	Histopathology, immunohistochemistry	itraconazole at the dosage of 10 mg /ml every 24 h,+ surgical excision	Cure
	Italy [70]	Madurella pseudomycetomatis	Histopathology, molecular identification	Surgery + Itraconazole (10 mg/Kg/d) for 65 days.	Cure
	France [68]	*Cladophialophora bantiana*	Histopathology, Culture, molecular identification	Surgery + oral itraconazole associated with flucytosine	Cure
	German[80]	*Pseudallescheria boydii*	Histopathology, Culture, molecular identification	Itraconazole (30 mg/kg/day)	Increased
	USA [60]	*Curvularia geniculata*	Histopathology, Culture		
	UK [81]	Pseudallescheria boydii	Histopathology, Culture	Ketoconazole+Surgery	Died
	USA [82]	*Pseudallescheria boydii*	Histopathology, Culture	Surgery	Died
	Korea, [64]	*Pseudallescheria boydii*	Histopathology	Surgery	Died
	India[66]	*Aspergillus terreus*	Culture	antibiotics and hydrocortisones+Surgery	Cure
	South Africa, [67]	*Madurella mycetomatis*	Histopathology, Culture	initially comprised oral ketoconazole ('Nizoral', Janssen) 10 mg kg-t body weight, three times a day, for 5 days together with enrofloxacin + oral fluconazole (Pfizer) 50 mg day for 6 weeks +Sergury	Recurrent
	Taiwan [72]	*Cladophialophora bantiana*	Histopathology, Culture, molecular identification	liquid nitrogen cryotherapy every week and oral antifungal of itraconazole 5 mg kg, Surgery+oral itraconazole was given for 2 months after surgery	Cure
	Australia [65]	Curvularia species.	Culture	oral itraconazole at5mg/kg SID for 90 days+surgery	Recurrent
	UK [83]	*Penicillium duponti*.	Histopathology, Culture	10 g/kg itraconazole orally once a day+Surgery	Cure

Table 1. It summarizes and describes selected case reports of eumycetoma in animals and the use of various antifungals that have proved successful in various animal species

The first case of mycetoma in a dog was reported by Robinson [84] who submitted a case to the Seminar of the American College of Veterinary Pathologists in 1952 [84]. The affected animal, a 5-year-old pointer from Florida, had a mycetoma between the toes of the right front foot for over 2 years. Then, after that, Seibold reported one case involving the left foot of a 3-year-old greyhound from Florida [59]. The grains in these cases were dark brown in thin histological sections [84][59]. Followed by three cases of mycetomas caused by *Curvularia geniculata* were reported in dogs by Charles H. *et al* in 1957 [71]. Case one represented a 4-year-old Walker hound who was submitted for clinical examination in September 1954 with a mass in the interdigital spaces of the right front foot. A diagnosis of mycetoma with black grains was made by histopathology and culture, which revealed *Curvularia*

geniculate[71]. In case two, a dog submitted to the Veterinary Clinic of Texas in May 1946 with a tumor in the skin of the foot was diagnosed by histopathologic examination as a mycetoma caused by *Curvularia geniculate*. In case three, the lesions were present in the abdominal cavity of an adult female dog, and the causative agents were identified as white grains mycetoma [71]. Mycetoma is usually restricted to subcutaneous tissues; there have been only four reports of cases involving intra-abdominal lesions in dogs [71][67][85][83]. These were associated with the uterine stump and the caudal aspect of the right kidney, caused by *Curvularia geniculate, Madurella mycetomatis*, *Curvularia species*, and *Penicillium duponti*, respectively.

Valerie *et al* in 1984 described a mycetoma of the fourth tarsal bone of a 5-year-old spayed Corgi-cross bitch caused by the *Curvularia geniculata*. The condition was treated successfully by surgical excision, followed by chemotherapy using iodine, trimethoprim-sulphadiazine, amphotericin B, dimethyl sulphoxide, thiabendazole, and nystatin [65].

Francesca *et al* in 2001 described two cases of canine dermatophytic pseudomycetoma resulting in subcutaneous nodules. In case one, an 8-year-old male Chow Chow was presented with a 5-cm-diameter subcutaneous nodule on the ventral neck, of 2 months′ duration. The diagnosis of dermatophytic pseudomycetoma was based on histology, fungal culture, and immunohisto-chemistry as *Microsporum canis* [69].

In case two, a 4-year-old female Yorkshire Terrier was referred for evaluation of a 3-cm-diameter, subcutaneous nodule on the groin, close to the mammary gland. An excision biopsy of the mass was performed, and *Aspergillus fumigatus* was diagnosed based on histology and immunohistochemistry [69].

Pseudomycetomas caused by dermatophytic fungi should be distinguished from eumycetoma. Dermatophytic pseudomycetoma is a deep cutaneous and subcutaneous infection in which granulomatous reactions surround the dermatophyte hyphae. It was suggested that mycelial aggregates formed by dermatophytes are best referred to as ‘pseudogranules’ and that the term ‘pseudomycetoma’ should be applied to such dermatophyte infections.

The disease has been described previously in only cats, [86][87][88][89][90] humans [91][92] and horses. [93] Most reported cases of feline dermatophytic pseudomycetoma have occurred in Persians. *Microsporum canis* is reported to be the common organism isolated from cultured nodules, [86][87][88][89][90] but *Trichophyton mentagrophytes* was cultured from a pseudomycetoma in one case [94]. The pathogenesis of the pseudomycetoma is not clear, but some authors proposed that the mycelial elements escape from the hair follicle into the surrounding tissues where they aggregate and induce an immune response [91][92]. In contrast to the supposed traumatic origin of a mycetoma, the exact immunological mechanism responsible for the formation of the grains is not clear yet.

Ajello *et al*. [95] described the criteria to differentiate between grains formed by mycetoma and pseudomycetoma, which include: A sequential formation, characterized by the presence of small to large clusters of mycelial elements; the pseudograins surrounded by Splendore–Hoeppli reaction; characterized by the presence of fewer hyphal filaments; and lack of a cementing substance [95].

J. Guillot *et al* in 2004 reported a case of eumycetoma due to *Cladophialophora bantiana* in a 3-year-old male Siberian Husky dog living in France. The dog presented a tumefaction on the thorax and deformity of the second and third subjacent ribs, which were surgically removed [68].

Peng-Cheng *et al* in 2011 reported the second case of eumycetoma caused by *Cladophialophora bantiana* from a 5-year-old castrated male Maltese with lesions on the abdomen for 3 months′ duration. Small black grains were drained from the fistulae. The grains were collected by a sterile swab, and the diagnosis of eumycetoma was made by microscopic examination and culturing. It was identified as *Cladophialophora bantiana* by morphology. The isolated fungus was subjected to molecular identification by amplifying and sequencing ITS regions and 5.8 S ribosomal DNA with the primer pair of ITS1 / ITS4. The sequence was 100% identical to that of CBS100436 of *Cladophialophora bantiana* [72].

In 2009, a case of disseminated pseudallescheriasis in a German Shepherd bitch was presented. Bones (ilium, a rib, and phalanges), joints (elbow and acetabulum), and the surrounding tissues were the principal organs affected. In addition, *Pseudallescheria boydii* was isolated, in lower numbers, from the eye, kidney, lymph nodes draining the affected regions, and urine. The dog was euthanized. *Pseudallescheria boydii* was identified by morphologic characteristics and molecular techniques. Interestingly, while mycetoma cases have been observed after trauma such as thorn breaks,

operations, or especially in cases involving hysterectomies that were complicated by dehiscence of the sutures, disseminated infections caused by the fungus have been reported only in German Shepherd dogs [80]. This case had no apparent portal of entry or predisposing factors. This seems to be similar to what is known concerning dogs suffering from disseminated aspergillosis caused by *Aspergillus terreus* [66].

In 2022, a 2-year-old dog had a subcutaneous mass in the right thigh that was surgically removed in Italy. Grossly, black grains were visible and molecularly identified as *Madurella pseudomycetomatis* [70].

In summary, in dogs, the most common agents of eumycotic mycetoma belong to the Scedosporium/Pseudallescheria complex (seven cases) [15][18][80][60][81][82][96], followed by four cases of mycetomas caused by *Curvularia geniculata* [71][65], two cases by *Cladophialophora bantiana* [68][72], one case caused by *Curvularia lunata* [23], *M. mycetomatis* [67], *Microsporum canis* [69], *Aspergillus fumigatus* [69], *Aspergillus terreus* [66], and *Madurella pseudomycetomatis* [70].

On the other hand, actinomycetoma reports have been relatively rare. Differentiating between lesions caused by Actinomyces species as opposed to Nocardia species can be challenging, but it is important for better identification of the causative agents and for better prevention and treatment of infection [54][55][56][57]. Cytological and histopathological evaluation, in combination with culture and sensitivity testing, is recommended. For both organisms, histological sections stained with Gram stain reveal Gram-positive, branching, filamentous rods. Acid-fast staining can be used for differentiation, as Nocardia species are more commonly acid-fast while Actinomyces species and other anaerobic actinomycetes are not. However, culture of the organism is still required for a definitive diagnosis. Nocardia species are strictly aerobic, are usually cultured, and are frequently the sole isolate obtained from the sample. Actinomyces species are either facultatively anaerobic or strict anaerobes. Although they are usually cultured within 5-7 days, growth may require up to 4 weeks [97][98][99].

Actinomycetes are endogenous saprophytes on the mucous membranes of the oral cavity and gastrointestinal tract of mammals [97][98][99].*Actinomyces viscosus, Actinomyces odontolyticus, Actinomyces israelii, Actinomyces naeslundii*, and *Actinomyces bovishave* have been cultured from the dental plaque of dogs, and *Actinomyces hordeovulneris* and *Actinomyces denticolens* have been cultured from normal feline gingiva [100]. These opportunistic pathogens depend on mechanical disruption of normal barriers by disease or trauma [90]. Bite wounds [49] and foreign bodies are the most common routes of infection in both dogs and cats [97]. Swerczek *et al* described eight cases of canine actinomycosis and mentioned important criteria for the differentiation of actinomycosis from similar diseases, especially nocardiosis, on the basis of histopathologic findings [101]. Nocardiosis usually affects dogs less than a year old, whereas actinomycosis usually affects the oldest dogs. Also, actinomycosis is more common among the hunting breeds, possibly because of their greater exposure to soil-contaminated trauma.

The first case of canine nocardiosis was apparently recorded by Trolldenier in 1903 [102]. Since then, several further cases have been reported. The disease in dogs is manifested with a variety of clinical presentations. The cutaneous or subcutaneous form of the disease, which simulates human mycetoma, shows purulent draining sinuses producing tomato soup-like exudates [51][56].*Nocardia otitidiscaviarum* was isolated from eight cases of cutaneous-subcutaneous lesions and one case of pneumonia in dogs in 2008 from Brazil [57]. The cutaneous-subcutaneous lesions (abscesses) in eight dogs were characterized by firm to fluctuant masses, with multiple draining sinuses, and exudation of serosanguinous to purulent secretions containing whitish granules (“sulfur granules”), predominantly in the cervical and inguinal regions of the skin [57]. In some animals, regional lymph nodes were affected. *Nocardia otitidiscaviarum* was predominantly isolated from the dogs, which were reported in seven cases, with *Nocardia asteroids* in one case. Great similarity was observed between the Nocardia species identified in the dogs and cattle, with isolates described previously in human nocardiosis [103][104][105][106][107].

Feline Mycetoma

Reports of mycetoma in cats are rare. However, to our knowledge, there is no reliable description of feline eumycetoma in the literature. A single case of a British feline eumycetoma is described in 1987 [78]. The lesions principally affected the soft tissues of the right hip and right sublumbar region and were characterized by granulomatous swelling with sinuses, discharging pus containing black granules *Exophiala jeanselmei* (*Torula jeanselmei*). *Exophiala* is a member of the dematiaceous

or brown-pigmented fungi and it has been isolated from soil in England [108]. It is probable that the infection in this cat was derived from soil and introduced into the body by wound contamination.

The dermatophytic mycetoma is uncommon in humans and animals [109]. As mentioned above, it is a unique form of dermatophytosis (pseudomycetoma).

The first case of feline mycetoma caused by a dermatophyte was reported in 2008 by Kano *et al*. The patient was a 9-year-old castrated male Persian cat weighing 4.2 kg with subcutaneous nodules on the dorsal trunk that drained purulent exudates with cement-like substances containing yellowish granules. The etiologic fungus was molecularly as well as morphologically identified as *Microsporum canis* [77].

Although pseudomycetoma has been described previously in cats, [86][87][88][89][90] humans [91][92] and horses. [93], most reported cases of feline dermatophytic pseudomycetoma have occurred in Persian cats, suggesting a genetic association with the disease, and *Microsporum canis* is reported to be the common organism isolated from cultured nodules, [86][87][88][89][90] but *Trichophyton mentagrophytes* was cultured from a pseudomycetoma in a single case [94].

For actinomycetoma cases in cats, individual case reports of actinomycetoma caused by Nocardia species and Streptomyces species have been reported [97][98][99]. It is more common for causative agents of feline mycetoma. *Nocardia asteroides* is the most common species isolated, and the other *Nocardia* species are very infrequently isolated [99][110]. Zoonotic infection in nocardiosis was not demonstrated until 2014 by Sykes [111]. However, nocardiosis has been reported in humans with profound scratch or bite wounds from healthy cats or dogs, so it has been considered a zoonotic disease.

There are 17 cases of nocardiosis in cats over 14 years from the three eastern states of Australia that have been reported [112]. The majority of cats presented with spreading lesions of the subcutis and skin associated with draining sinus tracts. Lesions were generally located in regions subjected to cat bite or scratch injuries, including limbs, body wall, inguinal panniculus, and nasal bridge. In some other cases, lesions were situated on distal extremities. Interestingly, the majority of infections were attributable to *Nocardia nova* [112].

In a single case report, *Nocardia africana* was first reported as an agent of mycetoma in a cat [58]. The clinical isolate was identified by physiological tests and 16S ribosomal DNA analysis [58].

Nocardia brasiliensis is an important cause of mycetoma in humans in the tropical areas of the Americas [33][50], and has also been recorded in a cat in California [113].

In cats, individual case reports of cutaneous and subcutaneous infections caused by Actinomyces species have been reported previously [114][115]. *Actinomyces viscosus, Actinomyces meyeri, Actinomyces pyogenes*, and *Actinomyces bowdenii* are the most common species isolated from cats [97][98][99][100][116]. Only a single report describing an intraperitoneal mass caused by Actinomyces in this species could be found in the literature [117]. In contrast, intra-abdominal actinomycetomas are more frequently reported in humans, predominantly affecting the ileocaecal junction. An unusual presentation of an abdominal actinomycetoma in a cat is described [118]. A 5-year-old, female Ragdoll cat was diagnosed with an intra-abdominal mycetoma involving the ileocaecal region [119].

Streptomyces species infections are rarely reported in cats, with three reports describing subcutaneous mycetomas. The first report was in the scapula of one cat [118], and the other affected a hind limb in another cat, which was identified as *Streptomyces griseus* [120]. The third case of orbital actinomycotic mycetomas in an 18-month-old male cat presented with an 8-week history of progressive unilateral right-sided mucopurulent nasal discharge and exophthalmos. *Streptomyces cinnamoneus* was identified as the causative agent [121].

Streptomyces cinnamoneus, a gram-positive, branching filamentous bacterium, belongs to the genus Streptomyces and the order Actinomycetales. Mycetomas due to Streptomyces species are clinically indistinguishable from those due to Actinomyces species [118]. Streptomyces species are slow-growing saprophytes that are prevalent in tropical and subtropical regions [122]. Infection is usually established after traumatic implantation [123][124]. Trauma is apparently necessary to produce conditions suitable for the growth of the agent. Since contaminating bacteria are commonly found in the lesions, these may be necessary "associates" for the actinomycete [33]. The collagenase activity of Streptomyces species is a risk factor that produces conditions suitable for the growth

and spread of the organism [123][124] to adjacent tissues, and an actinomycotic mycetoma is formed. [116][118]. Soft tissue infections can progress to involve bone over time. Infection is usually characterized by tumefaction and draining sinuses with granules or grains [123].

Mycetoma in Horses

Mycetomas in horses have been reported mostly in North America, South Africa, and Australia, and only once in Europe [29]. There were 17 publications reporting cases as eumycetoma in horses, with the etiological agent identified by culture or immunological techniques (Table 1). Among these, three cases [19][20] [125] were caused by *Bipolaris spicifera* (*Helminthosporium spiciferum* or *Curvularia spicifera* at the time of publication). The isolates from the remaining cases were identified as the Scedosporium/ Pseudallescheria complex (SPC), *Aspergillus versicolor, Curvularia verruculosa, Phialophora oxyspora*, and *Madurella mycetomatis*. [16][22][24][26][27][28][29][126][73][75][76].

These organisms can usually be isolated from plant material and soil; in particular, the Scedosporium/ Pseudallescheria complex (SPC) can also be isolated from polluted aquatic environments, salt water, and air [29].

Johnson *et al*, in 1975, described a case of a 13-year-old crossbred gelding from east-central Alberta (Canada), which was presented to the clinic at the Western College of Veterinary Medicine in June 1973 with a retrobulbar swelling causing severe exophthalmos of the left eye. *Scedosporium apiospermum* was isolated as the disease cause [14].

In 1977, Boomker *et al* reported the first case of mycetoma from South Africa, with black grain mycetoma occurring in two horses; in both cases, the organisms were identified as *Curvularia geniculata* [13].

In 1995, a 5-year-old mare was presented for treatment of a mass on the upper lip; fungal culture revealed all isolates were identical strains of *Aspergillus versicolor* [26].

A 2-year-old Jersey heifer was presented to Veterinary Clinics, Faculty of Veterinary Sciences and Animal Husbandry, Shere-Kashmir University of Agricultural Sciences and Technology of Kashmir, Srinagar, with a history of cutaneous dermatomycosis. Mycological screening of skin scrapings led to the isolation and identification of *Curvularia spp*. [126].

Elad *et al*, in 2010, reported a case of a 3-year-old Haflinger mare from Israel. It was presented with a wound, measuring about 3 cm, located on the left hind foot at the fetlock. Black 'granules' measuring up to 0.5 cm were seen in the wound. A biopsy was taken for histopathology and culture. The definitive identification of the isolate was established by molecular methods as Madurella *mycetomatis* [29].

Randleff-Rasmussen *et al* described the unusual finding of a cutaneous mycetoma on the right upper lip and lateral wing of the nostril of a 16-year-old horse in 2017. The causative agent was identified as *Aspergillus terreus* [27].

Mycetoma in Goats

In 1978, Gumaa *et al* reported for the first time in the literature three cases of mycetoma in goats [127]. Two goats had mycetomas on their hind legs, and the third had one on its left scapula. In two goats, the causative agents were identified by culture, histopathology, and serology as *Actinomadura madurae.* In the remaining goat, the diagnosis was based only on histopathology, and the causative agent was considered to be *Actinomadura pelletierii*. To our knowledge, there is no more reliable description of goat eumycetoma in the literature.

Mycetoma in Cattle

Drechslera rostrata was isolated from a case of eumycotic mycetoma with lesions involving the skin, nasal cavity, and lymph nodes of a cow. This represented the first case of eumycotic mycetoma in Australia. *Drechslera rostrata* is a ubiquitous fungus which often occurs on grasses and in the soil. It has not been isolated from other recorded cases of mycetoma [79].

Antifungal in Animals With Mycetoma Infections

The two major factors for the successful management of mycetoma patients are better identification of the causative agents and better prevention and treatment of infection [9][10]. The identification of the causative agent is valuable for proper treatment and identification of the drug of choice for patient treatment [10]. Especially, fungal mycetoma is difficult to treat, with long treatment durations and high recurrence rates.

For the treatment of eumycetoma, there are no standardized therapies; however, many of the antifungal agents that are used in humans are also used in animals for the treatment of eumycetoma infections. Itraconazole (ITC), voriconazole (VRC), posaconazole (POS), terbinafine, and the echinocandins demonstrate the most consistent in vitro activities against the relevant group of fungi [128][129][130][131][132][133][134][135][136][137].

Similarly, many limitations also occur in some animal species, including variable pharmacokinetics, adverse effects, drug interactions, and antifungal resistance.

Successful management of eumycetoma infection usually relies on wide surgical excision of affected areas after medical treatment with antifungal agents. Although antifungal therapy alone may result in a variable prognosis, even within strains of a single species, recurrence at the same or a new site is common [138].

Several treatment regimens have been employed for eumycetoma in animals by different authors. There are several reports on the use of itraconazole in veterinary medicine, and usually, a prolonged treatment of 1-2 years is required [139]. Treatment is continued after apparent clinical recovery to ensure that no fungal elements may remain at the site of healed lesions for up to 6 months.

In one report, a 10-month course of itraconazole (ranging from 10 mg/kg every 12 h to 20 mg/ml every 48 h), together with surgical excision, was successful in resolving dermatophyte pseudomycetoma in a cat [90].

In another case report, the use of oral itraconazole was promising as it was effective in reducing the size of the mass, but it had to be withdrawn because of gastrointestinal toxicity. Side effects have been reported in cats; they seem to be dose-dependent and are usually resolved after drug withdrawal [140].

For feline eumycetoma treatment, itraconazole 10 mg/kg/day is the treatment of choice but may or may not be successful. Alternatives include ketoconazole 10 mg/kg/day or terbinafine 30-40 mg/kg/day [141], and they should be combined with surgical removal.

No extensive clinical trials are available in veterinary medicine allowing us to correlate clinical and histological parameters with the response to therapy. The extension of the lesion, fibrosis, and oedema might be considered as factors influencing antifungal therapy.

Actinomycetomas are usually susceptible to antibiotic treatment. Several antibiotics, among these cotrimoxazole, streptomycin, trimethoprim, rifampicin, and amoxicillin-clavulanic acid combination, have been used and found to be effective [142][143][144][145]. In addition, combinations such as amikacin with cotrimoxazole and rifampicin, and meropenem have also been used. *In vitro* sensitivity of actinomycetes to ciprofloxacin and linezolid [146] has also been demonstrated, but these are currently not used as first-line therapy. Today, the common consensus is that cotrimoxazole should be administered as the gold standard therapy in all actinomycetoma patients. Combination antibiotic therapy is preferable to monotherapy to avoid the development of drug resistance and to eradicate residual infection. Surgery may be required for some patients unresponsive to medical therapy alone.

In 1987, Welsh demonstrated an excellent therapeutic response with amikacin alone and in combination with TMP-SMX (Welsh regimen) in the treatment of 15 patients with poorly responsive actinomycotic mycetoma and those with systemic involvement. The regimen included cyclical dosing of amikacin at 15 mg/kg/day, in two divided doses in cycles of 21 days for 1-3 cycles, with intervals of 15 days between cycles, while cotrimoxazole (one DS tablet BD) was administered continuously for 35-105 days. The 2-week interval of amikacin in the 5-week cycle is used for renal and audiometric monitoring. All patients achieved remission with this regimen, with most patients requiring two cycles (42 days) of amikacin and 70 days of cotrimoxazole therapy [147].

Raman*et al*. initially described a two-step regimen consisting of an intensive phase with penicillin, gentamicin, and cotrimoxazole for 5-7 weeks, followed by maintenance therapy with amoxicillin and cotrimoxazole continued 5-6 months after clinical remission; however, they later modified this to gentamicin (1.5 mg/kg IV) plus TMP-SMX (two DS tablets) given twice daily for 4 weeks, followed by continuation of TMP-SMX plus doxycycline (100 mg twice daily). This modified approach had the advantage of reducing the number of injections and the duration of the intensive phase and reducing the cost of therapy but still maintaining efficacy [148][149].

In case of resistance or allergy to co-trimoxazole or amikacin, co-amoxiclav can be used as an alternative to co-trimoxazole and netilmicin to amikacin. Co-amoxiclav can also be used alone during pregnancy; however, chances of resistance are there. Amikacin combined with a carbapenem, such as imipenem or meropenem, could also be used in refractory cases [150].

In conclusion, transmission by bites or scratches, mainly from cats, which can carry large amounts of spores between their claws in addition to their close contact with humans, may act as a risk factor for infection. Suspicious lesions should be biopsied for histopathologic examination and for culture and molecular identification; laboratory errors in the identification of the organism can occur. Tissue and exudate samples must be considered potentially hazardous until a definitive diagnosis has been made. For the treatment of eumycetoma, there are no standardized therapies; however, many of the antifungal agents that are used in humans are also used in animals for the treatment of eumycetoma infections. Clinical trials are needed in veterinary medicine to correlate clinical and histological parameters with the response to therapy.

Statements and Declarations

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