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Review

Disseminated canine mold infections

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ABSTRACT

Disseminated canine mold infections are reviewed. Case inclusion criteria were dogs as hosts, two or more non-adjacent organs affected and identification of the etiological agent at least to the genus level. Of the 157 cases identified, 59.3% were caused by *Aspergillus* spp. of which 36.3% belonged to the section *Terrei*. German Shepherd breed dogs constituted 67.8% of the cases, 89.7% of which were caused by fungi of the section *Terrei*. Female dogs constituted 72.7% of the cases. The average age was 4.3 years (range 1–13 years). Pathogenesis, especially virulence factors facilitating the hematogenous dissemination, are discussed. Clinical signs reported most frequently included weight loss, lethargy, discospondylitis, osteomyelitis, urinary tract infections, ophthalmitis, head tilt and gait difficulties. Of 50 dogs with data on temperature, 25 had a fever of 40 °C (104 °F) or above. The most common hematologic and biochemical test result aberrations included increased neutrophil counts and serum protein concentration, azotemia and decreased urine specific gravity. The diagnostic value of fungal antigen detection, antibody titers and imaging are discussed. An attempt to treat was made in 59 (37.6%). Failure and relapses (sometimes after years) were common, but there was some success observed in eight cases. Identification of the gene/s predisposing dogs to disseminated mycoses, increased awareness, improved diagnostic methods and less expensive drugs should contribute to the reduction of disseminated mold infections in dogs in the future.

Introduction

Disseminated fungal infections may be caused in dogs by yeasts such as *Cryptococcus* spp, dimorphic fungi (*Sporothrix* spp., *Histoplasma* spp., *Blastomyces* spp., *Coccidioides* spp. and, exceptionally, *Paracoccidioidomyces brasiliensis*) (Seyedmousavi et al., 2017) and molds. This review focuses on the latter. A group of mycoses, eumycetomata, have clinical characteristics such as a granulomatous reaction and 'granule' formation. While mostly subcutaneous, fungi belonging to the *Pseudallescheria/Scedoporium* complex may cause visceral mycetomata (Elad, 2011). Since the above-mentioned characteristics differ from those of the infections covered by this review, mycetomata have not been included. Publications were identified by looking for the keywords "dog", "canine", "systemic", "disseminated" and "mycosis". In a second search, genera of fungi that were the etiological agent of disseminated canine mycoses in the first search and the keyword "mucormycosis"; "zygomycosis"; "hyphomycosis"; "hyalohyphomycosis" and "phaeohyphomycosis" were added.

The inclusion criteria were as follows: (1) canine cases; (2) involvement of two or more non- contiguous organs (Berry and Leisewitz, 1996); and (3) the fungus was identified at least to the genus level by classical or molecular methods or by immunohistochemistry.

Seventy-seven publications describing 90 cases of disseminated mold infections in dogs were identified (Jang et al., 1971; Patnaik et al., 1972; Hay et al., 1978; Wood et al., 1978; Newsholme and Tyrer, 1980; Marks, 1983; Mullaney et al., 1983; Patterson et al., 1983; Charles, 1989; Jang et al., 1986; Lomax et al., 1986; Littman and Goldschmidt 1987; Baszler et al., 1988; Neer, 1988; Kahler et al., 1990; Wigney et al., 1990; Gelatt et al., 1991; Dallman et al., 1992; Salkin et al., 1992; Waurzyniak et al., 1992; Wilson and Odeon, 1992; Simpson et al., 1993; Kaufman et al., 1994; Schroeder et al., 1994; Kelly et al., 1995; Berry and Leisewitz, 1996; Pérez et al., 1996; March et al., 1996; Nakagawa et al., 1996; Thoma et al., 1999; Welsh and Ely, 1999; Robinson et al., 2000; Smith et al., 2000; Añor et al., 2001; Booth et al., 2001; Kano et al., 2002; Gene et al., 2003; Mackie et al., 2004; Bruchim et al., 2006; Singh et al., 2006; Zanatta et al., 2006; Erne et al., 2007; Elad et al., 2008, 2010; Holahan et al., 2008; Brockus et al., 2009; Grant et al., 2009; Poutahidis et al., 2009; Perry et al., 2010; Giri et al., 2011; Krockenberger et al., 2011; Tomlinson et al., 2011; Burrough et al., 2012; Haynes et al., 2012; Armstrong et al., 2012; Miller et al., 2012; Walker et al., 2012; Zhang et al., 2012; Armentano et al., 2013; Barrs et al., 2013; Sheppard et al., 2013; Sigler et al., 2013; Troy et al., 2013; Rizzo et al., 2014; Taylor et al., 2014; Cook et al., 2015; Dunlap et al., 2015; Kawalilak et al., 2015; Ribas et al., 2015; Taylor et al., 2015; Acierno

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et al., 2016; Ballhausen et al., 2016; Erles et al., 2018; Rothenburg et al., 2017; Bennett et al., 2018; Magstadt et al., 2018; Spano et al., 2018).

Six publications, for a total of 67 cases, were partially included (Kabay et al., 1985; Watt et al., 1995; Foley et al., 2002; Schultz et al., 2008; Sigler et al., 2010; Corrigan et al., 2016) since they were presented as one cohort and thus association between variables was either partial or not possible. These cases were included in the total counts (i.e. number of infections caused by *A. terreus*) but not associations (i.e. between breed and etiology).

Nineteen articles (Van den Hoven and McKenzie, 1974; Isoun, 1975; Peet and Robertson, 1976; Weitkamp, 1982; Oxenford and Middleton, 1986; Migaki et al., 1987; Pastor et al., 1993; Butterworth et al., 1995; Clercx et al., 1996; Carpenter et al., 2001; Evans et al., 2004; Sutton et al., 2008; Hugnet et al., 2009; Siemieniuch et al., 2009[1]; Bentley et al., 2011; Gershenson et al., 2011; Tappin et al., 2012; Zanoni et al., 2012) and 11 cases from clusters (Watt et al., 1995; Thoma et al., 1999; Schultz et al., 2008; Foley et al., 2002; Taylor et al., 2015) were excluded because the diagnosis was based exclusively on histology or there was a sole infection site.

History and nomenclature

The first case of what may be considered a disseminated canine mold infection (DCMI) was published in 1971 (Jang et al., 1971). The fungus was identified as *Paecilomyces* spp. in a Weimaraner. The first reported case of "classical" DCMI (a German shepherd dog infected with *Aspergillus terreus*) was reported by Wood et al. (1978). Interest rose in the 1980s and 1990s, including a series of publications by a single research group (Day et al., 1985, Day and Penhale 1988a,b, 1991) that tried to solve the question of the factors predisposing German Shepherd (GS) breed dogs to DCMI. Subsequently the number of publications abated, probably because most cases were not novel.

The reviewed cases are spread over several decades. Throughout this period, the names of several fungi have changed due to, among others, the application of state-of-the-art molecular technologies. This led to either the division of polyphyletic groups into several genetically more homogeneous species, as has happened to the *Scedoporium/Pseudallescheria* complex (Gilgado et al., 2008), or to their reclassification (i.e. *Scedosporium inflatum* to *Lomentospora prolificans*) (Ramirez-Garcia et al., 2018). In the former cases it was not possible to know to which of the newly defined species the original isolate belonged and thus the name used in the review is the one published in the respective report. In the latter cases, or when the name of a specific fungus was changed for other reasons such as the 'one fungus – one name' policy, the new names were used.

Etiology

Aspergillus terreus caused 55/175 (35%) of the reviewed cases. Two additional cases were caused by *Aspergillus carneus* and *Aspergillus alabamensis*. Phylogenetic studies have shown that *Aspergillus* section *Terrei* includes the species *A. terreus sensu stricto*, *A. carneus*, *Aspergillus niveus*, *A. alabamensis*, and *A. terreus* var. *aureus* (Escribano et al., 2012). These species are morphologically indistinguishable and can only be identified by molecular techniques. Since such means were not available at the time of earlier publications, some of the cases reported as being caused by *A. terreus*, might in fact have been caused by other members of the section *Terrei*. Consequently, if considered together, aspergilli of this group were involved in 57 (36.3%) of the cases. Other *Aspergillus* spp. were involved in 36 (23%) cases, included *Aspergillus deflectus*, *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus flavus*, *Aspergillus flavipes*, *Aspergillus felis* or unspecified *Aspergillus* spp. (Table 3). Analogously to *A. terreus*, fungi identified by classical methods as *A. niger* or *A. fumigatus* could belong to other, more recently described species, comprised in the *A. niger* complex or fungi of the section *Fumigati*. Thus, in combination, *Aspergillus* spp. were isolated from 59.3% of the cases. Other molds reported as etiological agents of disseminated canine mycoses included *Acremonium* spp., *Bipolaris spicifera, Bipolaris* spp., *Chrysosporium* spp., *Cladophialophora bantiana* (*Cladosporium trichoides, Xylophyla bantiana*), *Cladosporium cladosporioides-complex, Geomyces spp., Geosmithia argillacea*, *Lomentospora* (*Scedosporium*) *prolificans*, *Monocillium indicum, Ochroconis gallopava, Oxyporus corticola, Paecilomyces* spp., *Paecilomyces variotii*, *Penicillium purpurogenum*, *Penicillium* spp., *Penicillium verruculosum*, *Phialemonium obovatum*, *Phialosimplex caninus, Plectosphaerella cucumerina, Lecythophora canina, Pseudallescheria boydii*, *Schizophyllum commune, Scopulariopsis chartarum, Scytalidium* spp., *Spiromastix asexualis, Sporotrichum pruinosum, Talaromyces helicus, Tropicoporus* (*Inonatus*) *tropicalis,* and *Westerdykella spp.* for a total of 64 (40.7%) cases (Table 1).

Geographic distribution

Based on the first reports, Kaufman et al. (1994) suggested that a hot, humid climate may be a risk factor for DCMI. In the subsequent years, however, cases were reported from many parts of the world. The geographic distribution of publication numbers is shown in Tables 2 and 3. It is likely that the geographic distribution of the cases stems more from the interest of the local researches than the actual environmental conditions. Nevertheless, it is noteworthy that cases of DCMI with *A. terreus* as etiological agent were reported from Australia, South Africa, Israel and the US. Furthermore, for *A. terreus*, all the cases in the US, except for one (Michigan), were reported from states located under the 40th parallel (Table 3).

Breed, age and sex predisposition

Among the 112 cases in which breed and etiology could be matched (Table 1), GS dogs are clearly overrepresented (67.8% of the cases). This is especially manifest in dogs infected with fungi belonging to the section *Terrei* where GS constitute 89.7% of the cases.

Sex was reported in 150 cases. Females were clearly overrepresented (72.7%). Spaying/castration did not seem to pose a significant risk factor (Table 4).

Ages, reported for 97 dogs, were between 1 and 13 years. Mean, median, mode and standard deviation values were 4.3, 4, 4 and 2.07 respectively, indicating a normal distribution.

Pathogenesis

The portal of entry used by the fungus is usually unknown. This might be the result of the long delay between infection and mycological examination, usually after unsuccessful therapy attempts by private practitioners (Zhang et al., 2012). Thus, by the time the correct diagnosis is made, dissemination of the fungus has advanced to a point that makes an assessment of the evolution of infection impossible. The pathogenic cycle most likely starts with the deposition of fungal conidia from the environment in the

[1] See: Van Wie., E., Chen, A.V., Thomovsky, S.A., Tucker, R.L., 2013. Successful long-term use of itraconazole for the treatment of aspergillus diskospondylitis in a dog. Case Rep. Vet. Med. https://doi.org/10.1155/2013/907276. (Last accessed 15 October 2018).

Table 1
Fungal species associated with disseminated canine mycoses and breeds of infected dogs.

Fungus	GS	Other	Unknown	Reference
Aspergillus terrei gr. (*A. terreus* *n* = 55; *A. carneus* *n* = 1; *A. alabamensis* *n* = 1)	35	4	18	Wood et al. (1978), Mullaney et al. (1983), Kabay et al. (1985), Charles (1989), Neer (1988), Gelatt et al. (1991), Dallman et al. (1992), Wilson and Odeon (1992), Kaufman et al. (1994), Kelly et al. (1995), Watt et al. (1995), Berry and Leisewitz (1996), Thoma et al. (1999), Bruchim et al. (2006), Elad et al. (2008), Burrough et al. (2012)[d], Taylor et al. (2015), Corrigan et al. (2016)
Aspergillus deflectus	8	1	11	Jang et al. (1986), Kahler et al. (1990), Smith et al. (2000), Robinson et al. (2000), Krockenberger et al. (2011), Zhang et al. (2012)[d], Bennett et al. (2018)
Aspergillus fumigatus			3	Schultz et al. (2008), Corrigan et al. (2016)
Aspergillus *niger*			2	Schultz et al. (2008)
Aspergillus flavus		1		Thoma et al. (1999)
Aspergillus flavipes			1	Schultz et al. (2008)
Aspergillus felis			1	Barrs et al. (2013)
A. versicolor			1	Corrigan et al. (2016)
Aspergillus spp.	4		3	Marks (1983), Pérez et al. (1996), Walker et al. (2012), Perry et al. (2010), Corrigan et al. (2016)
Acremonium spp.	2	1		Hay et al. (1978), Simpson et al. (1993), Ballhausen et al. (2016)
Bipolaris spicifera		2		Waurzyniak et al. (1992), Rothenburg et al. (2017)[d]
Bipolaris spp.		1		Giri et al. (2011)[d]
Chrysosporium spp.	2			Watt et al. (1995), Cook et al. (2015)
Cladophialophora bantiana		3		Newsholme and Tyrer (1980), Schroeder et al. (1994), Añor et al. (2001)
Cladosporium cladosporioides-complex	1	1		Poutahidis et al. (2009)[d], Spano et al. (2018)[d]
Geomyces spp.		1		Erne et al. (2007)
Geosmithia argillacea	1	1		Grant et al. (2009)[d], Kawalilak et al. (2015)[d]
Lomentospora prolificans[c]	1	3		Salkin et al. (1992), Haynes et al. (2012), Taylor et al. (2014), Erles et al. (2018)
Monocillium indicum[a]		1		Mackie et al. (2004)
Ochroconis gallopava		1		Singh et al. (2006)
Oxyporus corticola	1	1		Miller et al. (2012)[d], Brockus et al. (2009)
Paecilomyces spp[a]	4	3	5	Jang et al. (1971), Patterson et al. (1983), Watt et al. (1995), Littman and Goldschmidt (1987), March et al. (1996), Nakagawa et al. (1996), García et al. (2000)[b], Foley et al. (2002)
Paecilomyces variotii	2	2		Booth et al. (2001), Patnaik et al. (1972), Holahan et al. (2008)
Penicillium purpurogenum	1			Zanatta et al. (2006)
Penicillium spp.	3			Watt et al. (1995), Acierno et al. (2016)
Penicillium verruculosum	1			Wigney et al. (1990)
Phialemonium obovatum	2			Lomax et al. (1986), Smith et al. (2000)
Phialosimplex caninus	1	3		Sigler et al. (2010)[d], Sigler et al. (2013), Armstrong et al. (2012)[d]
Plectosphaerella cucumerina and *Lecythophora canina*	1			Troy et al. (2013)[d]
Pseudallescheria boydii	3			Watt et al. (1995), Baszler et al. (1988), Elad et al. (2010)[d]
Schizophyllum commune		1		Kano et al. (2002)[d]
Scopulariopsis chartarum		1		Welsh and Ely (1999)
Scytalidium spp.	1			Dunlap et al. (2015)[d]
Spiromastix asexualis	1			Rizzo et al. (2014)[d]
Sporotrichum pruinosum		1		Magstadt et al. (2018)[d]
Talaromyces helicus		1		Tomlinson et al. (2011)[d]
Tropicoporus tropicalis		2		Ribas et al. (2015)[d], Sheppard et al. (2013)[d]
Westerdykella spp.	1			Armentano et al. (2013)[d]

GS, German Shepherd or German Shepherd mix breed.
[a] Reclassified as *Phialosimplex chlamydosporus* (Sigler et al., 2010).
[b] Reclassified as *Sagenomella chlamydospora* (Gene et al., 2003) followed by *Phialosimplex chlamydosporus* (Sigler et al., 2010).
[c] Formerly *Scedosporium prolificans*.
[d] Publications with molecular identification.

respiratory system. In human medicine, the dissemination depends in most cases from the lack of suitable macrophage and/or neutrophil reaction in immune-compromised patients (Margalit and Kavanagh, 2015). Since such deficiencies have not been individuated in the large majority of dogs affected by DCMI, the factors that predispose them to this condition remains, with a few exceptions (see below), unknown.

Table 2
Geographic distribution of publications (countries).

Country	Publications (*n*)	Isolate
USA	58	See Table 3
Australia	12	*A. terreus, A. flavus, A. carneus, A. deflectus, Aaspergillus* spp., *P. boydii, Lomentospora prolificans, Chrysosporium* spp., *Penicillium* spp., *Paecilomyces* spp., *Monocillium indicum*
Israel	2	*A. terreus, P. boydii*
South Africa	6	*A. terreus, Acremonium* spp., *Paecilomyces varioti, Cladophialophora bantiana*
Spain	2	*Aspergillus* spp., *Sagenomella chlamydospora*
UK	1	*L. prolificans*
Italy	2	*P. purpurogenum, Cladosporium cladosporioides-complex*
Canada	2	*Paecilomyces* spp., *Phialosimplex caninus*
Japan	2	*Paecilomyces* spp., *Schizophyllum commune*
Germany	1	*Acremonium* spp.
Greece	1	*Cladosporium cladosporioides* – complex

Table 3
Geographic distribution of publications (US states).

State	Publications (*n*)	Isolates
California	17	*A. terreus, A. deflectus, A. fumigatus, A. niger, A. flavipes, Aspergillus* spp. *Paecilomyces* spp., *Cladophialophora bantiana*
Texas	6	*A. terreus, A. deflectus, A. fumigatus, A. alabamensis, Aspergillus* spp., *Bipolaris* spp.
Virginia	5	*A. terreus, Aspergillus* spp., *Geosmithia argillacea, Plectosphaerella cucumerina, Lecythophora canina, Oxyporus corticola*
Florida	5	*A. terreus, Aspergillus* spp., *Geomyces* spp., *Tropicoporus tropicalis, Westerdykella* spp.
Minnesota	3	*Penicillium* spp., *Bipolaris spicifera*
Oklahoma	3	*B. spicifera, Scopulariopsis chartarum, Ochroconis gallopava*
Louisiana	2	*A. terreus, Tropicoporus tropicalis*
Michigan	2	*A. terreus, P. variotii*
New York	2	*Paecilomyces variotii, L. prolificans*
Alabama	2	*Phialemonium obovatum, Talaromyces helicus*
Georgia	2	*A. terreus, Phialemonium obovatum*
Ohio	1	*Acremonium* spp.
Pennsylvania	1	*Paecilomyces* spp.
Tennessee	1	*A. terreus, A. fumigatus, A. versicolor, Aspergillus* spp.
Missouri	1	*Paecilomyces* spp.
Maryland	1	*Phialosimplex caninus*
Iowa	1	*Phanerochaete chrysosporium* (teleomorph of *Sporotrichum pruinosum*)
Arizona	1	*Spiromastix asexualis*
Nevada	1	*Oxyporus corticola*
Illinois	1	*Pseudallescheria boydii*

Table 4
Distribution of infected dogs by their sex.

Total female	109	72.7%	Spayed	60	55%
Total male	41	27.3%	Neutered	22	53.7%

Mechanisms of the dissemination of *A. terreus* were the ones most extensively studied. This fungus, along with other fungi of the sections *Flavipedes* and *Jani* produce, both in vivo and in vitro, special pleomorphic propagules, defined as accessory spores or aleuriospores. These differ from the phialidic conidia, among other characteristics, by growing directly on the hyphae and by being produced not only in cultures but in the infected tissue as well (Deak et al., 2009). Other fungi involved in CDMI, including *Paecilomyces* spp. and fungi belonging to the *Scedosporium/Pseudallescheria* complex, however, have been reported to produce in vivo conidia defined as 'adventitious forms' (Liu et al., 1998). Both these and the accessory spores facilitate hematogenous dissemination and it was suggested that the spores are blocked at sites of capillary loops or other sites of blood flow speed reduction such as kidneys or vertebrae, thus making these organs the most frequently affected by disseminated mold infections (Kabay et al., 1985).

It was suggested previously (Wood et al., 1978) that awn migration may be a source of DCMI. While this may be true in a very small proportion of cases, inhalation remains the most likely portal of entry in most cases (Walker et al., 2012). Additional, less common, portals of entry may be the gastrointestinal tract (Kabay et al., 1985) or the skin (Ballhausen et al., 2016). In one case (Elad et al., 2008), uterine invasion preceded the appearance of neurological signs, and thus this organ might have acted as the portal of entry.

Clinical signs

Signs were described in 123 cases. General malaise was reported most frequently – 74 (60.2%) of the cases, including weight loss, with or without anorexia and lethargy. Ataxia and other gait abnormalities were reported in 52 (42.3%) of the cases, resulting either from central nervous system (CNS) involvement, discospondylitis (DSP) and/or osteomyelitis, mostly of the extremities. These cases are accompanied by various grades of pain, demonstrable by palpation, localized around the axial and/or the musculoskeletal region affected by mycosis. Eyes and CNS were affected more rarely in 21 (17.1%) and 34 (27.6%) cases, respectively, with no predominant fungal species involved. CNS involvement is usually accompanied by head tilt and lack of balance. These dogs are often treated initially for otitis that may cause similar clinical signs. Gastrointestinal signs (vomiting and/or diarrhea) were reported in 16 cases, 6 of which were GS/GS mixed breed dogs.

Details of the localization of the affected vertebrae for individual dogs were provided in 26 cases. The infection showed a clear predilection for the thoracic and lumbar areas, especially noticeable in GS dogs (Table 5). The vertebral area involved may indicate the spread of the fungus: the area/s most frequently affected may be also the most likely to be the first ones reached by the fungus. Thus, the more frequent involvement of the thoracic and lumbar vertebrae might indicate the respiratory and/or the digestive system as the main portals of entry for the infective agent. Of the 31 cases in which the vertebral lesions could be matched to a fungus species, 11 (35.5%) were identified as *A. terreus*, eight (25.8%) as other *Aspergillus* spp. and 12 (38.7%) as non-*Aspergillus* spp. Sternebrae were affected in six cases.

Pyrexia was reported in 50 cases. Twenty-five dogs (50%) had a fever of 40 °C (104 °F) or above, 13 (26%) had a temperature between 39.3 °C and 39.9 °C (102.7 °F and 103.8 °F) and twelve dogs (24%) were afebrile (39.2 °C/102.6 °F or lower). Body temperature was, however, not constant: it might have been normal at presentation but increase in subsequent days or be

Table 5
Regions of axial skeleton affected.

Vertebrae involved	Cases (*n*)	GS
Cervical only	2	1
Cervical and thoracic	1	1
Thoracic only	5	4
Thoracic and lumbar	8	7
Lumbar only	4	4
Lumbar and sacral	0	
Cervical, thoracic and lumbar	5	3
Thoracic, lumbar and sacral	1	1
Total cervical	8	5
Total thoracic	18	13
Total lumbar	17	14
Total sacral	1	1

GS, German Shepherd or German Shepherd mix breed.

intermittent. There was no association between etiology and body temperature.

Diagnosis

In general, hematological and biochemical test anomalies result from the inflammatory process and the organs affected and do not specifically indicate the nature of the infection. The most common hematologic and biochemical test result aberrations include increases in neutrophil counts, serum protein concentration, azotemia due to high creatinine and urea levels, and a decrease in urine specific gravity (Schultz et al., 2008).

The most commonly used non-invasive, convenient and inexpensive ante mortem test is the microscopic examination and culture of urine. Of 33 cases in which such tests were performed, 28 (84.9%) were positive. In the relatively rare cases of ocular involvement, an ophthalmoscopic examination may reveal chorioretinitis (Baszler et al., 1988) and hyphae may be microscopically detected and/or cultured from the vitreous (Gelatt et al., 1991). CSF characteristics, reported relatively rarely, do not differ from those of other infections or neoplasia and their sensitivity for fungal culture is low (Taylor et al., 2015).

In human medicine, a commercial kit (Platelia Aspergillus, BioRad) which detects fungal cell wall antigen, galactomannan (GM), in sera and bronchoalveolar lavage fluid, is in use. In humans, this assay has an overall sensitivity ranging from 40 to 71% and specificity ranging from 53 to 89% (Garcia et al., 2012). A few reports of testing the value of this kit for the diagnosis of canine disseminated aspergillosis have been published. Garcia et al. (2012) tested the GM kit on sera and urine of 13 dogs with proven and 37 with suspected disseminated aspergillosis and 52 uninfected control dogs. Proven cases had significantly higher values than suspected or control animals. Sensitivity and specificity were 92% and 86%, respectively, for serum and 88% and 92%, respectively, for urine. Increasing the cutoff values from 0.5, recommended for human samples, to 1.5, raised the specificity of the test to 93% without impacting the sensitivity. Taylor et al. (2015), while testing the clinical and the magnetic resonance aspects of seven dogs with disseminated aspergillosis, performed the GM test on three of them. Values above 6 were obtained (significantly higher than the recommended 0.5). A temporary decrease of the index was observed in one dog, under antimycotic therapy, that underwent serial measurements. Treatment with fluid replacement (Plasmalyte, Baxter Health) or beta lactam antibiotics may induce false positive results (Taylor et al., 2015). Corrigan et al. (2016) assessed the efficacy of posaconazole treatment for canine disseminated aspergillosis. Four dogs were positive at presentation and two of these had serial GM tests. One of these dogs relapsed after an initial period of apparent remission, whereas the other one was cured. GM index levels became negative in the latter, while remaining high in the former. While the results seem promising, the number of animals is very low and definitive conclusions will have to be drawn after further experiments.

The anti-*Aspergillus* antibody titer has a diagnostic and prognostic value in some forms of human aspergillosis (Page et al., 2015) but its significance in CDMI has not been elucidated. One of the limitations of the test in human medicine stems from the serum antibody concentrations being below the limits of detection in immunocompromised patients. Serological results in dogs with CDMI have been variable. For example, Day and Penhale (1988a) reported that GS dogs with CDA had increased IgG titers, while Schultz et al. (2008) reported that four of five dogs tested negative for *Aspergillus* antibodies using an agar gel antibody immunodiffusion test. In one study in upper respiratory tract mycoses in cats, Barrs et al. (2015) reported that IgG titers were sensitive and specific for the diagnosis of infection. No similar studies in dogs have been identified while preparing this review. Consequently, serological tests for canine aspergillosis should be complemented with other tests before reaching a conclusive diagnosis (Bentley et al., 2018).

The value of imaging techniques in CDMI was assessed by several authors. Magnetic resonance imaging (MRI) in seven dogs, six of which had CNS fungal infections, did not detect any abnormalities in three dogs and identified pathological changes that varied in the remaining animals (Taylor et al., 2015). Schultz et al. (2008) examined three dogs with neurological signs using MRI and observed multifocal brain lesions in the cerebral hemispheres ($n = 3$), in the brainstem ($n = 2$) and a mass in the cerebrum of one dog. Thus, dogs with CNS dissemination of molds lacked typical MRI images present in similar infections in humans.

Digital radiography of dogs with fungal DSP demonstrated osteolysis, endplate destruction and collapse of the intervertebral disc (Weitkamp, 1982; Kawalilak et al., 2015). Mycotic and bacterial DSP cannot be differentiated without microscopic or cultural examinations. Other microorganisms, especially dimorphic fungi must be excluded, especially in endemic areas. *Brucella* spp. may cause DSP, osteomyelitis and/or arthritis and, considering the significant zoonotic hazard infected animals can pose (unlike these infected with molds), the necessary precautions must be taken while being exposed to them, pending identification of the etiology of the infection.

Post mortem examinations may reveal the extent of the affected organs and the histopathologic characteristics of the lesions. The latter consist mostly of pyogranulomata that include giant multinucleate cells and hyphae and other fungal elements (Watt et al., 1995) thus confirming the diagnosis of mycotic infection. Accessory conidia may be present, depending on the etiology. A culture and molecular classification of the fungus is necessary to complete the diagnosis. It is noteworthy that for an accurate identification of the etiological agent, characterization of the ITS gene may not be enough, and one or more additional gene/s, such as calmodulin and/or the tubulin need to be sequenced (Burrough et al., 2012).

The early diagnosis of DCMI is of the essence for a prompt initiation of antifungal therapy. Unfortunately, there are no pathognomonic signs and thus most cases are treated for other clinically similar ailments that are more frequent. In some cases, dogs are submitted to several such treatment cycles, resulting in the dissemination of the fungus by the time the correct diagnosis is made. The solution of this problem probably lies in an increased awareness to the possibility of a fungal etiology and the performance of suitable test (according to the organ affected), some of which are relatively straightforward (i.e. microscopy and/or culture of aspirations from affected discs, CSF, lymph nodes or urine). Although false negative results are possible, especially at the microscopic examination, the application of these tests (preferably in combination) could lead to the early detection of many dogs with DCMI.

Therapy

By the time the dogs are presented to specialized clinics, they are likely to have been treated with a variety of drugs; some of which, such as steroids, are contraindicated in fungal infections. Thus, the fungus is already in an advanced stage of dissemination (Zhang et al., 2012) making the prognosis poor. In addition, some of the fungi involved, especially *A. terreus*, are intrinsically resistant to antimycotic drugs that act on the metabolism of ergosterol This may be due, at least partially, to the low content of this substance in their plasma membrane (Deak et al., 2011). Moreover, some of the more recent drugs are prohibitively expensive for veterinary use,

especially considering the fact that they have to be administered for long periods, sometimes for the rest of the dog's life. Consequently, therapy was instated in only 59 (37.6%) cases (if the therapy duration was less than 7 days, except for amphotericin B, they were considered as untreated). Of these, the therapy failed, the dogs were lost to follow up or the infection relapsed after it was terminated in 53 (89.8%) cases. Relapses occurred sometimes more than a year after therapy cessation (25 months in one case described by Schultz et al., 2008) thus the possibility of reinfection due to individual predisposition cannot be excluded. Six dogs (10.2%) qualified as cured at the time of their case publication (Table 6). Three of these cases were last examined less than a year after therapy cessation. Considering that some of the relapses were observed years after therapy termination, this might not be enough to qualify these cases as microbiologically cured. Two dogs (Erne et al., 2007; Sigler et al., 2013) recovered clinically but not mycologically (the etiological agent persisting in the affected organs) after being treated with itraconazole.

The drugs used were amphotericin B ($n = 5$) ketoconazole ($n = 11$), itraconazole ($n = 36$) fluconazole ($n = 7$), voriconazole ($n = 5$), posaconazole ($n = 14$; 10 were from one study), various lipid formulations of amphotericin B ($n = 11$), hamycin ($n = 1$), terbinafine ($n = 10$) and caspofungin, anidulafungin and micafungin ($n = 1$) (Elad, 2018). These drugs were administered alone or in combinations, concurrently or sequentially, due to lack of improvement. Some of these drugs (such as the lipid formulations of amphotericin B) are prohibitively expensive and thus may be considered only under experimental conditions and/or for a limited time. For other drugs (voriconazole, caspofungin) the patent has expired or will expire in the next few years (posaconazole, micafungin, anidulafungin). For the former, generic products are available at prices lower than the original preparations. However, the expenses stemming from the necessity of protracted, possibly life-long, treatments still hamper their adoption on a large scale.

Antimycotic drugs are not devoid of toxicity, especially considering the long periods they must be administered. Ketoconazole, the first systemic azole (imidazole) available for veterinary use, was associated with a variety of adverse effects, such as hepatotoxicosis and the inhibition of testosterone production (Papich et al., 2001). The later azoles (triazoles) such as itraconazole and flucanozole can be usually administered with mild or no side effects (Bennet, 2005). *Aspergillus* spp., however, is almost always resistant to the latter and fluconazole is thus not recommended for treatment of aspergillosis (Odds et al., 1986). The experience with newer drugs such as voriconzole, posaconazole and the echinocandins is currently limited. As mentioned above, the effectiveness of amphotericin B, often useful in treating cases of aspergillosis, is limited against *A. terreus* due to its intrinsic resistance to the drug (Deak et al., 2011). In addition, it has been associated with side effects, most markedly nephrotoxicity. Various preparations of the drug aimed at reducing its toxicity have been devised, but their use in veterinary medicine is limited by their price (Nieto et al., 2018).

Fungal susceptibility testing has become common in human medicine, especially since standard interpretations of the results have been formulated by the Clinical Laboratory Standards Institute, currently in its 3rd edition (CLSI, 2017). For antibacterial drugs, standards specific for veterinary use have been published (CLSI, 2018). Since no such standard for antimycotic drug susceptibility currently exist, the extent to which human standards are applicable in veterinary medicine, considering the anatomic and physiologic differences between humans and animals and between different animal species, is unclear (Miller et al., 2012). Moreover, the variety of antifungal drugs available for the treatment of mycotic infections in animals is significantly more limited than that accessible for human cases. Thus, fungal susceptibility testing in veterinary medicine is performed only sporadically (Grant et al., 2009; Sigler et al., 2010, 2013).

Immunology

The GS breed is affected by several pathologies associated with immune deficiencies (Tengvall et al., 2013). The risk factors predisposing GS dogs to disseminated aspergillosis have been investigated in several studies. Most canine IgA is produced in the intestine (Day and Penhale, 1988a). Thus, abnormalities in its peripheric levels are likely to reflect enteric anomalies in the metabolism and/or function of this group of immunoglobulins. Deficits in IgA functions in GS dogs were reported for (probably) the first time in relation of enteric dysbiosis occasionally afflicting this breed by Whitbread et al. (1984). They reported that blood IgA, but not IgG or IgM, levels were significantly lower in GS dogs. These findings were later confirmed by Batt et al. (1991) who reported that the relative deficit of IgA was not related to a lower number of cells producing the immunoglobulin and consequently likely to result from diminished production or secretion. These findings were confirmed more recently by Lee et al. (2015).

In a series of publications, Day et al. (1986) and Day and Penhale (1988a,b, 1991) reported increased serum IgG titers and IgA anomalies in GS in general and those with disseminated mold infections in particular. Pérez et al. (1996) confirmed these findings and Littler et al. (2006) reported that IgA levels were lower in GS dog feces. Decreased IgA serum levels were, however, not reflected locally on the mucosae (Ginel et al., 1993). Interestingly, Berry and Leisewitz (1996), reported that two GS littermates, one of them with disseminated aspergillosis, had a weaker cell mediated

Table 6
Cases of apparently successful therapy.

Breed	Age (years)	Sex	Etiology	Treatment	Last examined	Reference
GS	7	M	*A. deflectus*	KC ~2 months	4 months after amputation	Jang et al. (1986)
RCK	8	FS	*A. terreus*	IC 17 months	3 years after therapy ended	Kelly et al. (1995)
GS	Unknown	Unknown	*A. terreus*	IC indefinitely	4 years after diagnosis	Watt et al. (1995)
GS	4	MC	*A. terreus*	VC, TF 11 months, LAmB 8d	11 months after therapy ended	Taylor et al. (2015)
GS	Unknown	Unknown	*A. terreus*	PC, TF 15 months	5 years after therapy ended	Corrigan et al. (2016)
GS	3	FS	*Plectosphaerella cucumerina* and *Lecythophora canina*	IC + TF	14 months after therapy initiation	Troy et al. (2013)

RCK, Red Cloud Kelpie; GS, German Shepherd; FS, female spayed; MC, male castrated; IC, itraconazole; KC, ketoconazole; PC, posaconazole; VC, voriconazole; TF, terbinafine; LAmB, liposomal amphotericin B.

immune response than a control dog, possibly indicating a genetic background behind the increased susceptibility of this breed.

Other than congenital immune defects, pathological or iatrogenic conditions may predispose to disseminated fungal infections. Among the cases included in this review, no data were provided on immune status for 72 (45.9%). Publications reporting 55 (35%) cases specifically stated that no predisposing factors were recorded. Immunosuppressive therapy was administered to 30 (19.1%) dogs. Some of these treatments may have predisposed the animal to the fungal infection or precipitated the evolution of the infection if administered after its onset. Unfortunately, it is not possible to distinguish between those two possibilities. A pathological state, treated with immune-suppressive medication, that existed before the diagnosis of disseminated mycosis was documented in only nine dogs (5.7%) cases: pruritic dermatitis (Wilson and Odeon, 1992), immune-mediated thrombocytopenia (Schultz et al., 2008; Rothenburg et al., 2017), immune mediated hemolytic anemia (Armstrong et al., 2012; Taylor et al., 2014), inflammatory bowel disease (Singh et al., 2006), atopy (Ribas et al., 2015) and Imerslund-Gräsbeck syndrome (Erles et al., 2018).

During the last decade, significant advances have been made in the mechanisms of host-parasite interactions at the molecular level. Among these is the discovery of specific pattern recognition systems such as the toll-like receptors (TLRs). These have been associated with enteric IgA production in humans (Liang et al., 2011) and a mouse model (Shang et al., 2008). In dogs TLR polymorphism was connected to chronic enteric infections of GS dogs (Allenspach et al., 2010; Kathrani et al., 2010, 2011; Lee et al., 2015). Moreover, TLR polymorphism is considered a risk factor for invasive aspergillosis in human transplant patients (Koldehoff et al., 2013). Thus, it is conceivable that TLR polymorphism that increases the susceptibility of the GS breed to enteric diseases, and has been linked to human IgA production and invasive aspergillosis, may also be the basis of its predisposition to canine disseminated mycoses, especially in GS.

Future prospects

To advance the management of disseminated mold infections, the gene/s responsible for the increased susceptibility of the GS breed should be identified. This would enable dogs carrying these genes to be excluded from the pedigree registers (as has been done for many years for dogs of the same breed with hip dysplasia). In addition, since early diagnosis may improve the likelihood of therapeutic success and improve animal welfare, DCMI should be included more often in differential diagnosis lists; a means to identify affected animals also needs to be developed. Finally, the price of the most state of the art antimycotic drugs is expected to decrease, making them available for veterinary use.

Conflict of interest statement

The author of this paper has no financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

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