Temporary remission of disseminated paecilomycosis in a German shepherd dog treated with ketoconazole

M J Booth[a*], J J van der Lugt[b], A van Heerden[c] and J A Picard[d]

ABSTRACT

Disseminated mycosis caused by *Paecilomyces varioti* in a female German shepherd dog presented with chronic forelimb lameness is described. Radiographs of the swollen carpal joint revealed geographic lysis of the radial epiphysis. Diagnosis was based on cytological demonstration of fungal hyphae and chlamydiospores, as well as fungal culture of fluid obtained by arthrocentesis. Temporary remission was characterised by markedly improved clinical signs and laboratory parameters, following treatment with ketoconazole. The dog was euthanased 9 months after the initial diagnosis, following the diagnosis of multifocal discospondylitis. This appears to be the longest described period of temporary remission obtained with treatment in dogs with paecilomycosis. Clinical, clinicopathological and necropsy findings of this disease in another German shepherd dog are briefly described.

Key words: arthritis, discospondylitis, German shepherd dog, hyalohyphomycosis, *Paecilomyces varioti,* ketoconazole, osteomyelitis.

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INTRODUCTION

Paecilomyces is an opportunistic soil-living saprophytic fungus, regarded as non-pathogenic, and an occasional laboratory contaminant. Fungal infections have been reported in humans[2,15,19,20], 8 dogs[5,7,9–11,13,14,18], a cat[4] and other species[4,10]. Two additional cases of suspected *Paecilomyces* spp. infections have been described in dogs[3,17]. Paecilomycosis is a fatal disease in dogs and cats, and 30 of 46 human cases had a negative outcome[2].

Staphylococcus aureus or *S.intermedius* is usually the cause of discospondylitis in dogs, with fungal agents being uncommon[6]. Discospondylitis is frequently diagnosed in large-breed dogs, affecting twice as many males as females[6]. Fungal discospondylitis is, however, not uncommon in the German shepherd dog (GSD) and is believed to be due to the presence of an immunocompromised state[6,18]. Discospondylitis caused by *Paecilomyces* spp. has been described in 3 dogs[5,7,13] and suspected in a 4th[14].

The purpose of this paper is to describe the clinical course of *Paecilomyces varioti* in a German shepherd dog and its temporary remission with ketoconazole. A second case of paecilomycosis in a GSD is briefly described.

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CASE HISTORY

Case 1

A 5-year-old neutered female GSD (37.8 kg) was referred with a history of lethargy, general weakness, anorexia, weight loss and left forelimb lameness of 6 weeks duration. Mild carpal swelling and grade 2/4 lameness had been noticed a few days before seeking veterinary advice. The dog was treated with oral phenylbutazone (Inflazone, Pharmador) that temporarily resolved the lameness. Radiographic examination 12 days later (Fig. 1) showed a diffuse, uniform, poorly-demarcated 8 mm soft tissue swelling over the lateral aspect of the left carpus and distal ulna. A well-defined 11 × 15 mm area of focal geographic lysis was present laterally in the distal radial epiphysis. Aspiration revealed haemorrhagic fluid, but cytology was not performed. Subsequent treatment with oral prednisolone (Lenisolone, Pharmador) and lincomycin (Lincocin, Upjohn Pharmaceuticals) did not result in any improvement. The dog had no history of having received high dose or long-term immunosuppressive drugs.

At the time of referral to the Onderstepoort Veterinary Academic Hospital

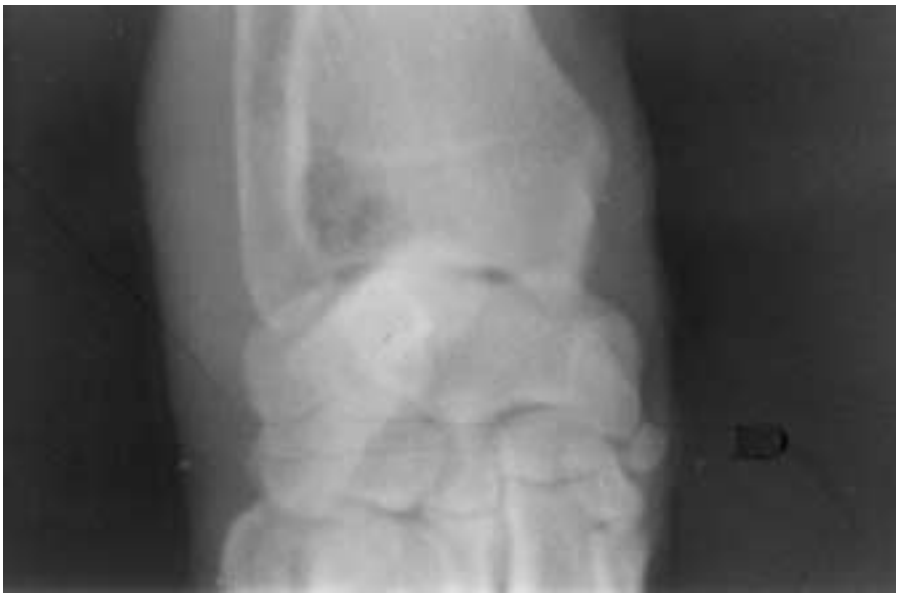

Fig. 1: **Radiograph of the left carpus made by the referring veterinarian showed a poorly defined soft tissue reaction and focal geographic lysis.**

(OVAH), a grade 3/4 lameness was present, with slight crepitation of the left carpal joint. A hard, slightly painful distended area was palpated over the dorsolateral carpus with a softer area dorsomedially. Rectal temperature was 39.2 °C with slight lymphadenopathy of the ipsilateral prescapular lymph node. Radiographs (Fig. 2) showed a marked, well-defined, focal, 9 mm soft tissue reaction from the distal antebrachium to the carpo-metacarpal joint dorsally and the middle carpal joint laterally. The craniodistal radius had a 2–5 mm irregular, thick brush-like periosteal reaction. There was marked cortical thinning of the distal radial epiphysis and metaphysis, eroding the subchondral bone. The area of geographic lysis had a honeycomb appearance and measured 23 × 25 mm. A 1–3 mm irregular, thick brush-like periosteal reaction extended for 35 mm along the distal ulna laterally, separated from the cortex by a 1 mm radiolucent line proximally. The radiocarpal and ulnar bones were unaffected. Thoracic radiographs and abdominal ultrasonography were regarded as normal.

Arthrocentesis of the radiocarpal joint yielded bloody material with a low viscosity, a specific gravity of 1.035, a protein concentration of 65 g/ℓ, and large amounts of coagulated, granular eosinophilic fibrin deposits. Nucleated cell numbers were markedly elevated, consisting mainly of toxic, degenerate neutrophils and highly active macrophages with a tendency to aggregate. Numerous free and phagocytosed fungal hyphae and chlamydiospores were seen. Phagocytosed fungal elements were mainly in macrophages (Fig. 3), but also in a few neutrophils. Rosetting of neutrophils around the fungi was observed. The white blood count (WBC) was normal (11.4 × 10^9/ℓ). Slight hyperglobulinaemia (39.3 g/ℓ, reference range 20–37 g/ℓ), and mildly elevated alanine transferase (57 U/ℓ, reference range 4–40 U/ℓ) were present. The IgG (>5000 mg/dℓ, reference range 1000–2000 mg/dℓ) and IgM concentrations (400 mg/dℓ, reference range 100–200 mg/dℓ) were markedly elevated, while the IgA (50 mg/dℓ, reference range 40–160 mg/dℓ) concentration was normal.

Joint fluid was inoculated onto Sabouraud's dextrose agar (SDA) (Oxoid, England), mycobiotic agar (MA) (Labretoria, South Africa) and brain–heart infusion agar (BHIA) (Oxoid, England) and incubated aerobically at 25 °C (SDA, MA) and 37 °C (BHIA). After 3 days' incubation a pure, heavy mould growth was observed on all plates. Macroscopically the colonies were fluffy, cinnamon-coloured on the upper surface and tan below. Microscopic examination of lactophenol cotton blue staining of several slide cultures demonstrated the asexual vegetative fruiting bodies characteristic of *Paecilomyces varioti* (Fig. 4). *In vitro* testing showed strong sensitivity to flucytosine, cotrimazole, miconazole and nystatin, intermediate sensitivity to amphotericin B and resistance to griseovulvin. Ketoconazole sensitivity could unfortunately not be performed. Empirical treatment was started with ketoconazole (Nizoral, Janssen Pharmaceutica) at 10 mg/kg twice daily per os, with instructions to restrict exercise.

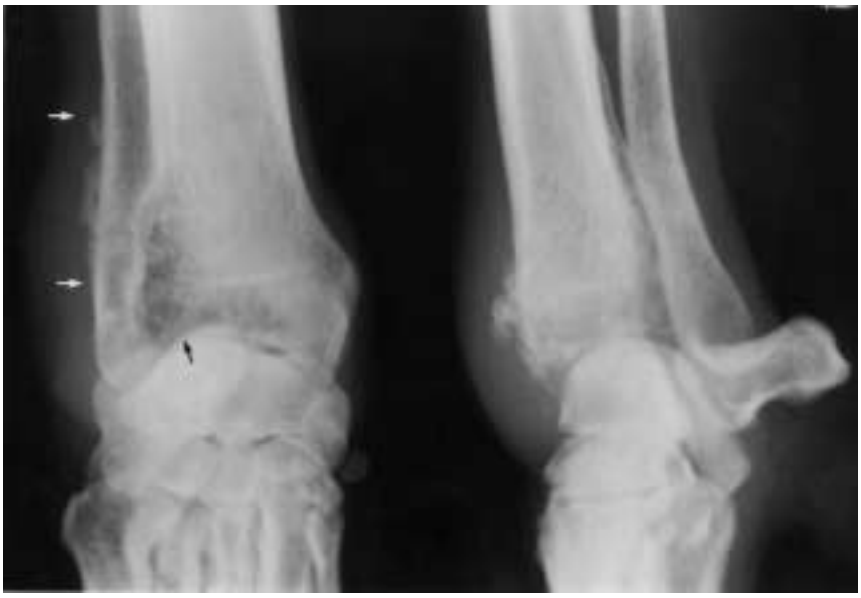

Fig. 2: **Radiographs made at referral 24 days later show increased lysis that had eroded the subchondral bone** (black arrow)**. An irregular, thick brush-like periosteal reaction is visible on the craniodistal radius, and along the distal ulna laterally** (white arrows)**.**

After 4 weeks on ketoconazole, the carpal swelling was unchanged, but the patient had started to take weight on the limb. Radiographs of the carpus (Fig. 5) demonstrated a slightly decreased soft tissue swelling, increased lysis with the caudolateral aspect of the distal radial epiphysis absent, and a 4 mm sclerotic zone. A 2–4 mm solid periosteal reaction extended 52 mm along the ulna. The WBC count was elevated (22.7 × 10^9/ℓ) owing to mature neutrophilia (17.71 × 10^9/ℓ). The joint fluid was turbid with a specific gravity of 1.031, a protein concentration of 50 g/ℓ, a total cell count of 57.15 × 10^9/ℓ and a nucleated cell count of 17.13 × 10^9/ℓ. No fungi were seen. Urinalysis was unremarkable, and blood, urine and joint cultures were negative for fungi. At 8 weeks,

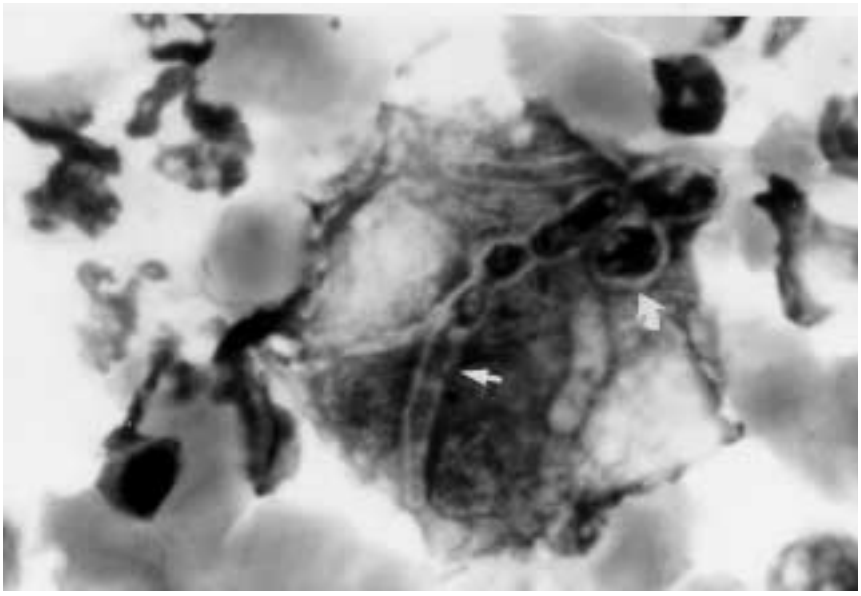

Fig. 3: **Cytological preparation of material obtained by arthrocentesis of the radiocarpal joint. Phagocytosed fungal hyphae** (white arrow) **and chlamydiospores** (curved arrow) **surrounded by a clear halo are visible within a highly active macrophage. Neutrophils and red blood cells are also present.** Romanowsky stain, ×1000.

crepitus had decreased, the joint swelling was hard and non-painful and the patient was sound on the limb. Urinalysis was unremarkable. A supportive modified Robert Jones bandage was applied for the following 11 weeks.

Nineteen weeks after initiating treatment no lameness was present, but reduced radiocarpal range of motion was present. Radiographs showed resolving osteomyelitis with decreased more uniform periosteal reactions, a diminished area of lysis, and absence of the sclerotic margin. After 6 months the dog was clinically normal, sound on the limb and had gained weight. Following negative blood and urine cultures, ketoconazole therapy was discontinued. Radiographs confirmed containment of the infection with new bone formation, indicating resolution of the lesion.

During routine follow-up examination 3 months after discontinuing therapy, spinal hyperaesthesia at T_5 and $T_{9–11}$ was noted. New bone formation around the area of original radial lysis was evident (Fig. 6). The $T_{6–7}$ disc space had widened to 8 mm with a 2 mm sclerotic zone and marked ventral non-bridging spondylosis. An early discospondylitic lesion at $L_{4–5}$ showed vertebral end plate lysis, widening of the disc space to 8 mm, a 3 mm sclerotic zone and no ventral spondylosis. A lesion at $T_{2–3}$ consisted of advanced ventral spondylosis and increased disc space without a sclerotic margin. An advanced lesion at $T_{10–11}$ showed a narrowed disc space, irregular sclerotic margin and prominent mature bridging ventral spondylosis (Fig. 7).

Owing to clinical and radiological signs of active multifocal suspected fungal discospondylitis, euthanasia was advised. Necropsy examination revealed generalised muscle atrophy and fibrous arthritis of the radiocarpal and intercarpal joints and fibrinopurulent tenosynovitis of the extensor carpi radialis tendons of the left forelimb. Granulomatous discospondylitis and spondylosis of $T_{2–3}$, $T_{6–7}$, $T_{10–11}$ and $L_{4–5}$ in conjunction with mild osteomyelitis of T_6, T_7, T_{10} and T_{11} were evident. The spleen, liver, hepatic and pancreatic lymph nodes contained multiple, focally disseminated granulomatous foci. Histological examination confirmed multifocal to coalescing granulomatous inflammation in the spleen, liver, lymph nodes, lung, myocardium, pericardium, and bone marrow. Weakly eosinophilic yeast-like organisms and occasional hyphae were seen in areas of inflammation in sections routinely stained by haematoxylin and eosin (HE). These organisms were clearly demonstrated with periodic acid-Schiff (PAS) as

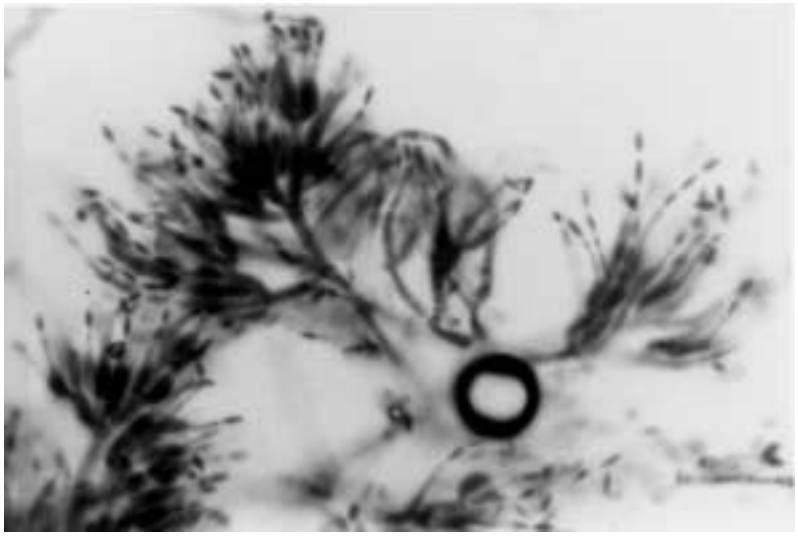

Fig. 4: **Slide culture showing asexual vegetative fruiting bodies of *Paecilomyces varioti.*** Lactophenol cotton blue stain, ×400.

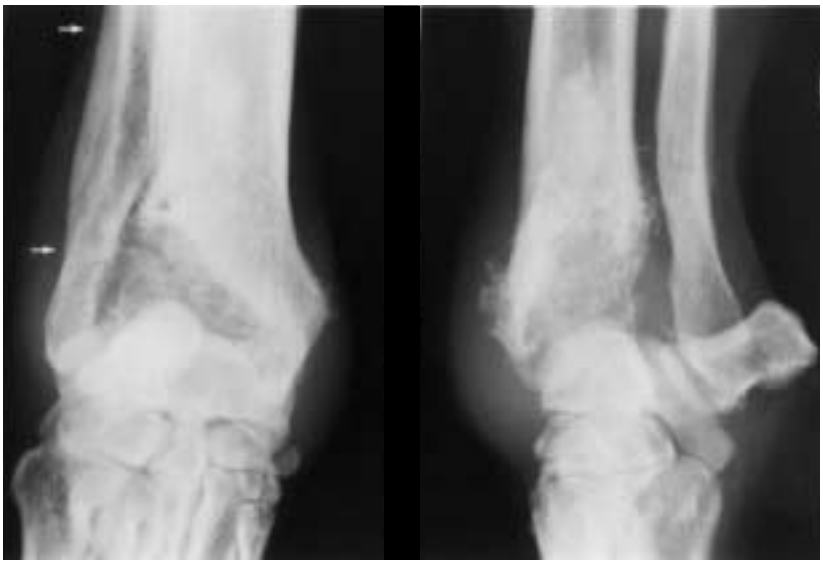

Fig. 5: **Four weeks after starting ketoconazole treatment, the area of lysis was more extensive and surrounded by a 4 mm sclerotic zone proximally. The caudolateral aspect of the radial epiphysis was absent and the lateral periosteal reaction had progressed to a solid reaction** (arrows) **extending proximally.**

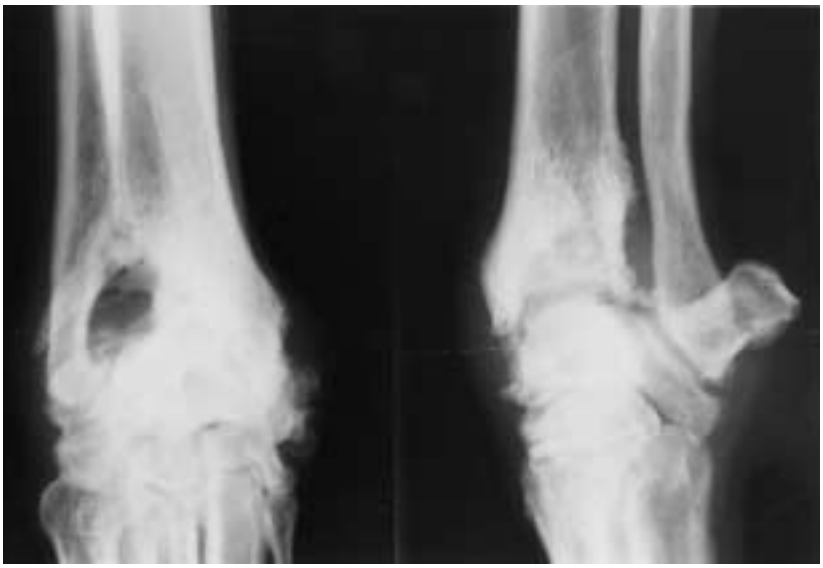

Fig. 6: **Nine months after diagnosis, the radiocarpal joint showed signs of osteo-arthritis and resolution of the osteomyelitis, with new bone formation in the previous area of lysis.**

intracellular round to ovoid yeast forms, approximately 2–15 µm in diameter, with thick walls and occasional single, broad-based budding. Fungal profiles were most numerous in the bone marrow (Fig. 8). A heavy growth of *Paecilomyces varioti* was obtained from the left axillary lymph node, kidney, liver, pancreatic lymph node and affected intervertebral discs, but not from the carpal joint, blood or urine.

Retrospective re-examination of the initial thoracic radiographs demonstrated the presence of discospondylitis. Irregular new bone formation was present ventral to $T_{2–3}$ and $T_{10–11}$, and the $T_{10–11}$ disc space was centrally widened to 5 mm due to end plate lysis (Fig. 9).

Case 2

A 6-year-old intact female GSD was referred to the OVAH with a history of gradual onset hindquarter paresis progressing to paralysis. The dog had a history of chronic allergic skin disease and otitis externa that was treated intermittently with corticosteroids and antibiotics. Depression, fever (39–39.4 °C) and cystitis had been present for 8 weeks before referral. At presentation the dog was emaciated, with hindquarter and bladder paralysis. Routine urinalysis revealed fungal hyphae on sediment analysis. Haematology demonstrated mild hyperchromic anaemia (RCC 5.05 × $10^{12}/\ell$), marked neutrophilia (WBC 54.1 × $10^9/\ell$, mature neutrophils 42.74 × $10^9/\ell$, immatures 6.49 × $10^9/\ell$), monocytosis (2.7 × $10^9/\ell$) and eosinopaenia (0.0 × $10^9/\ell$). Mild hyperglobulinaemia (40.8 g/ℓ) was present. The serum concentrations of phosphate (1.63 mmol/ℓ, reference range 0.9–1.6 mmol/ℓ), urea (17.6 mmol/ℓ, reference range 3.6–8.9 mmol/ℓ), creatinine (232 µmol/ℓ, reference range 40–133 µmol/ℓ) and amylase (2869 U/ℓ, reference range 200–1800 U/ℓ) were elevated. Survey radiographs of the vertebral column revealed active disospondylitis with varying degrees of disc space widening, ventral spondylosis and metaphyseal sclerosis at $T_{4–5}$, $T_{5–6}$, $L_{2–3}$ and $L_{3–4}$, with subluxation present at $L_{3–4}$. Cytology of fluoroscopy-guided fine-needle aspirates of the lumbar intervertebral discs demonstrated fungal hyphae and chlamydiospores. Fungal culture of this material failed to yield any growth. Owing to the poor prognosis, the dog was euthanased and a necropsy was performed. Extensive multifocal pyogranulomatous mycotic inflammation was present in the renal medulla and pelvis, regional lymph nodes, spleen, pancreas and $T_{4–5}$ and $L_{2–4}$ vertebral bodies and intervertebral discs. A heavy growth

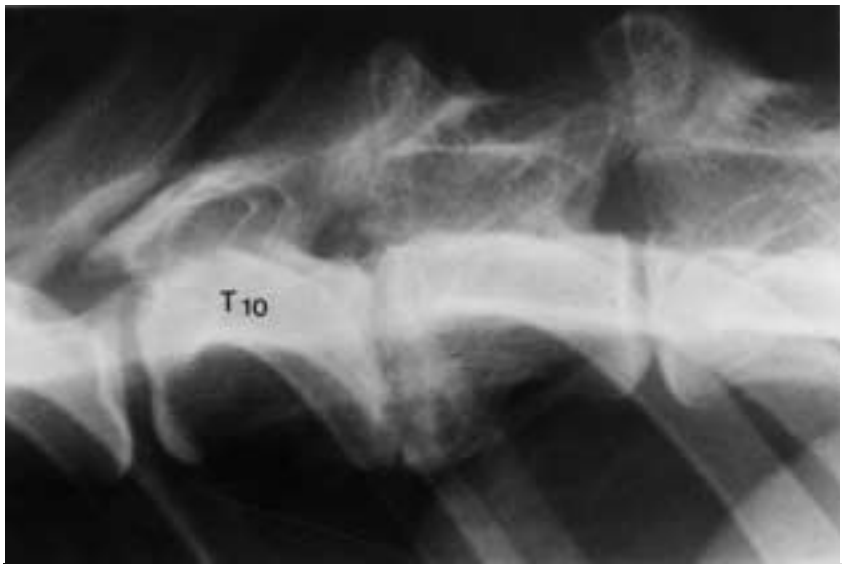

Fig. 7: **Appearance of the $T_{10–11}$ discospondylitis lesion. The disc space had collapsed and is bridged ventrally by uniform mature bone, indicating a resolved lesion.**

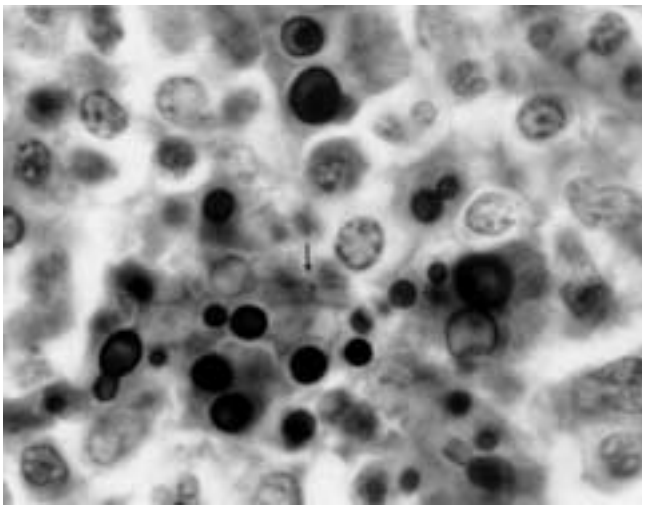

Fig. 8: **Intra-cytoplasmic yeast showing broad-based budding and a single hyphal element** (arrow) **in the bone marrow.** PAS, ×600.

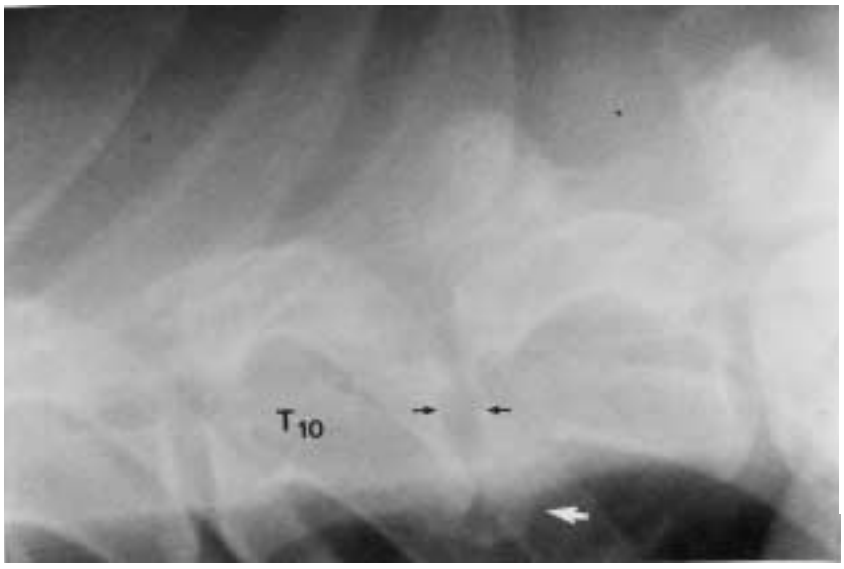

Fig. 9: **Initial thoracic radiograph showed central widening of the $T_{10–11}$ disc space** (black arrows) **and irregular new bone formation ventral to the disc space** (arrowhead)**.**

Table 1: **Summary of 12 confirmed and suspected cases of *Paecilomyces* spp. infections in dogs.**

Reference	Breed	Sex	Age in years	Suspected route of entry	Clinical signs	Treatment	Outcome
3	Dachshund	M	1½	–	Fever, seizures, ataxia, lymphadenopathy	–	Died
5	GSD cross	F	5	–	Depression, anorexia, weight loss, neck rigidity, relapsing otitis externa	Ketoconazole	Died 26 weeks
7	Weimeraner	F	4	Brachial plexus wound	Shoulder pain, fever, anorexia, ataxia, weakness	–	Euth
9	Cocker spaniel	F	7	Ventral abdomen scab	Exercise intolerance, cough, fever, anorexia, weight loss, depression, chorioretinitis, generalised lymphadenopathy	Ketoconazole	Euth 3 weeks
10	Viszla	F	3	Otitis externa	Anorexia, weight loss, colitis, deafness, ataxia, otitis externa, sublingual mass, chorioretinitis, lymphadenopathy	AmpB + ketoconazole Fluconazole Itraconazole	Euth 15 weeks
11	GSD	F	5	Ulcerated hock	Hock oedema, nasal erosions, ulcerated hock	Flucytosine + fluconazole	Euth 7 weeks
13	Mixed breed	F	7	–	Fever, depression, hemiparesis, swollen hock, chorioretinitis	Tetracycline	Euth 17 days
14	GSD	FN	4	Otitis externa	Fever, weight loss, deafness, PUPD, hindquarter weakness/ataxia, otitis externa, splenomegaly	–	Euth
17	Kelpie X	FN	1½	Ulcerated digit	Ulcerated digit, local lymphadenopathy, seizures	–	Died
18	GSD	NR	NR	–	NR	NR	NR
‡	GSD	FN	5	–	Forelimb lameness, anorexia, weight loss, fever, weakness, depression, swollen carpus, local lymphadenopathy	Ketoconazole	Euth 36 weeks
‡	GSD	F	6	–	Chronic otitis externa, fever, weight loss, chronic cystitis, depression, hindquarter paresis/paralysis, bladder paralysis	–	Euth

F = female; M = male; GSD = German shepherd dog; ‡ = present report; Euth = euthanased; FN = female neutered; AmpB = amphotericin B; NR = not reported.

of *Paecilomyces varioti* was isolated from the kidney, pancreas and vertebral discs.

DISCUSSION

A summary of the data from 10 previously reported confirmed or suspected cases of paecilomycosis in dogs, and the 2 cases in this report is presented in Table 1. The only breed represented more than once is the GSD (6 of 12). Females comprised 91 % (10 of 11) cases, and are overrepresented in reports of disseminated opportunistic mycoses. In a review of disseminated opportunistic mycoses, female involvement was reported in 9 of 10 cases[18], and in disseminated aspergillosis 77 % (10 of 13) cases were female[12]. All the dogs included in this review were adult, ranging in age from 1.5 to 7 years old (mean 4 years 5 months, median 5 years). This is in agreement with previous reports of opportunistic mycoses occurring exclusively in adult animals[12,18].

The ability of most fungi to invade tissues is dependent on the host's immune status. Most human cases of paecilomycosis have been associated with factors predisposing to opportunistic fungi, namely foreign body implants, trauma or immune incompetence[2]. The skin, alimentary and respiratory systems are considered to be important portals of entry[15]. Four of the 12 canine paecilomycosis cases had a history of open skin lesions and a further 4 had otitis externa or a history of relapsing otitis externa. The origin of the osteomyelitis and septic arthritis in Case 1 could not be determined, although the possibility of undetected trauma could not be ruled out. *Paecilomyces lilacinus* caused prepatellar bursitis in a human patient without a history of a break in the skin or foreign body penetration, after he started working on his knees on a cement floor[19]. It may therefore be possible for the organism to gain access through intact skin. It is speculated that the infection in this case spread from the joint, since radiographically the joint changes were the most advanced. If haematogenous spread from the respiratory or gastrointestinal system had occurred, a metastatic bone pattern would have been more probable.

Clinical signs seen with mycoses depend upon the organ systems involved. Neck or back pain, anorexia, weight loss and fever were the most common in 1 study[18]. The most common signs in 9 published cases in which clinical signs were reported[3,5,7,9–11,13,14,17] and the 2 cases reported here (n = 11) were fever (7), ataxia/paresis/paralysis (6), weight loss (6), anorexia (5), depression (5) and appendicular skeletal signs (5). In a study of osteomyelitis caused by systemic blastomycosis[16], 19 of 25 bone lesions were located in the long bones of the limbs, all distal to the elbow, and only 2 proximal to the stifle. The following bones were involved: radius (5), ulna (4) and tibia (4). Twelve of 19 lesions in the long bones were located in the metaphysis or epiphysis. This is similar to long bone involvement in disseminated aspergillosis in which the predilection site is the epiphysis, leading to secondary septic arthritis by direct extension[8]. The radiographic finding in blastomycosis is predominantly osteolysis with a periosteal or soft

tissue reaction, without fistulas or sinus tracts. In a previous report of *Paecilomyces* spp. affecting a joint, the hock was clinically swollen and the tibia showed an irregular periosteal reaction[13]. Necropsy revealed a marked periosteal reaction, with osteoid and granulomatous tissue, and exudate within the hock joint. Although no mention was made of stifle involvement, a positive culture was obtained at *post mortem*. Case 1 is suspected to have started as an osteomyelitis progressing to arthritis due to delayed treatment.

Pre-treatment urine and blood cultures were not performed in Case 1, but sequential urine cultures during treatment and at necropsy failed to yield any growth, despite positive cultures from numerous organs. Positive urine cultures were obtained in 6/6 dogs with disseminated mycoses before treatment, but hyphae were never observed in dogs receiving treatment[18]. During follow-up cultures and at necropsy, no fungi could be isolated from the carpal joint, indicating resolution of the infection from the joint. The decreased sclerotic zone, collapsed disc space and bridging spondylosis at $T_{10–11}$ indicated a radiographically inactive lesion[1] as was the case at $T_{2–3}$. The authors suggest that treatment with ketoconazole resolved the joint infection but only suppressed the discospondylitis, with active infection recurring when treatment was stopped. Active discospondylitis at $T_{6–7}$ and $L_{4–5}$ is presumed to have started after cessation of ketoconazole.

Species identification of *Paecilomyces* has only been reported in 2 other canine cases[9,13], both being *P. varioti.* Proper identification and sensitivity testing are important because *P. varioti* is susceptible to most common antifungals including amphotericin B and flucytosine, while *P. lilacinus* is generally highly resistant to these drugs[2,15,19]. In previous reports, *Paecilomyces* was found to be highly sensitive to Amphotericin B and flucytsine, with intermediate sensitivity to ketoconazole[9,10]. *P. varioti* was previously reported to be resistant to miconazole and griseovulvin[9]. The fungus described in this report was strongly sensitive to miconazole, to which *P. varioti* in another report showed resistance[9]. Resistance to griseovulvin was confirmed. Results of fungal *in vitro* sensitivity testing do not always correlate well with *in vivo* clinical response[2]. Ketoconazole has been used previously in 3 cases of paecilomycosis in dogs[5,9,10], in 2 cases as the only medical treatment, with 1 dog surviving for 3 weeks[9]. The duration of treatment of the dog in the 2nd report is uncertain[5]. Initial treatment was for 2 months, with complete clinical improvement after a month. Ketoconazole was then discontinued for a week, because the dog was vomiting, before being reinstituted. This dog died after 26 weeks. In the 3rd case, ketoconazole was combined with amphotericin B for the first 8 weeks, before being substituted by fluconazole because of its ability to cross the blood-ocular and blood-brain barriers[10]. Ketoconazole in this case was chosen empirically based on previously reported efficacy, cost and reduced toxicity with prolonged use.

This report confirms that female adult German shepherd dogs are predisposed to opportunistic disseminated fungal infections. Any dog of this breed diagnosed with a deep mycotic infection should be screened for discospondylitis and systemic spread of the disease. Scintigraphy would be a sensitive modality when available. Ketoconazole can be an effective treatment for *Paecilomyces* infection following culture and sensitivity testing. Antifungals may, however, need to be given for greatly extended periods in dogs with opportunistic disseminated mycoses. Hyphae were seen in the intervertebral discs of a dog after 21 months of treatment with itraconazole[18]. Only remission, and not cure, may be possible in these patients.

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