A case of *Trichophyton mentagrophytes* infection in a fennec fox (*Vulpes zerda*)

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A 2-year-old male fennec fox presented with a 4 month history of nonpruritic, crusty skin lesions on the forehead, the pinnae and the tail tip.

Initial investigations, including routine haematology, biochemistry profile, multiple skin scrapings, trichoscopic examination, Wood’s lamp examination and fungal culture, failed to reveal any abnormalities. Histopathological examination of a first set of skin biopsies showed an interface dermatitis pattern, with lymphocyte infiltration in the basal layer, a significant lymphocytic exocytosis and occasional apoptotic basal epidermal keratinocytes; periodic acid Schiff stain did not reveal any fungal elements. On further biopsies, there was a pustular neutrophilic dermatitis, with numerous crusts containing high numbers of arthrospores and fungal hyphae. *Trichophyton mentagrophytes* infection was confirmed on fungal culture and PCR.

The fennec fox received oral itraconazole (5 mg/kg once daily for 6 weeks) combined with a miconazole and chlorhexidine shampoo applied on affected areas once weekly, followed with an enilconazole dip. The fox improved dramatically, and a fungal culture performed at 6 weeks was negative. Unfortunately, a few days later the fennec fox developed anorexia, icterus and died.

To the authors’ knowledge, this is the first report of *Trichophyton* infection in a fennec fox and, although a post-mortem examination was not performed, this is possibly the first report of fatal acute liver failure associated with itraconazole in a canid.

Introduction

The fennec fox (*Vulpes zerda*) is a small nocturnal fox found in the Sahara desert, classified into the family *Canidae* of the order *Carnivora*. The fennec fox is the smallest species of *Canidae* in the world; coat, ears and kidney functions have adapted to a high-temperature, low-water and desert environment. The fennec fox’s fur is prized by the indigenous peoples of North Africa, and in some parts of the world the animal is considered an exotic pet. Fennec foxes are in Appendix II of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) and considered threatened in the wild. There is little reported in the veterinary literature regarding disease conditions of fennec foxes; therefore, new information regarding medical conditions in this species is of particular interest.

Case report

A 2-year-old, 1200 g, male fennec fox (*Vulpes zerda*) presented with a 4 month history of nonpruritic, crusty skin lesions on the forehead, the pinnae and the tail tip. He lived in a private zoo with a female, who did not have any skin lesions at the time of the consultation. There was a previous history of similar lesions on the bridge of the nose and the pinnae, which had not responded to empirical systemic griseofulvin and topical enilconazole 4 months previously. No other health problems were reported by the zoo keeper. Routine haematology and biochemistry profile had been unremarkable. The fennec was hospitalized in an individual kennel, and precautions were taken to avoid direct and indirect contact with other animals. A clinical examination did not reveal any abnormalities. Dermatological examination revealed alopecia and moderate erythema on the convex aspect of the pinnae and the ear margins. Numerous yellow crusts and large scales were additionally present (Figure 1); underneath these, the skin was bright and slightly exudative. Similar lesions, though less severe, were noted around the eyes, on the tail tip and on the bridge of the nose (Figure 2).

The initial differential diagnoses included parasitic infestations (demodicosis, leishmaniosisis), infectious dermatitides (*dermatophytosis, bacterial pyoderma*), primary cornification disorder (sebaceous adenitis), pemphigus complex and, less likely, cutaneous lymphoma.

Multiple skin scrapings and trichoscopic examination failed to reveal any mites or fungi. Wood’s lamp examination and fungal cultures (carpet square method) were

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negative. Microscopic examination of Diff-Quick stained impression smears revealed neutrophils with a few acantholytic cells and numerous coccoid bacteria. Oral cefalexin (Therios 60; Laboratoire Sogeval, Laval, France) 20 mg/kg twice daily was prescribed for 3 weeks, but lesions failed to improve. The fennec fox was then anaesthetized with isoflurane (ISOFLO 100%; Axience SAS, Pantin, France; induction via induction chamber and maintenance via facemask). Four 6-mm-punch biopsy samples were obtained from pinnal lesional skin and submitted for histopathological examination. There was epidermal regular acanthosis, laminated hyperkeratosis and mild multifocal spongiosis. An interface dermatitis with lymphocyte infiltration was observed in the basal layer. A significant lymphocytic exocytosis and occasional apoptotic basal epidermal keratinocytes were also present (Figure 3). In the dermis, a widespread interstitial infiltrate was mainly composed of plasma cells and macrophages. The specific periodic acid Schiff staining did not reveal any fungal elements.

Skin biopsies were collected 1 month later, with the same anaesthetic protocol. The histopathological findings were completely different. There was a pustular neutrophilic dermatitis with numerous crusts containing high numbers of arthrospores and fungal hyphae. The presence of fungal elements was confirmed with periodic acid Schiff staining (Figure 4).

Fungal culture of scales and crusts was also repeated and showed a growth of 10 colonies after 1 week. The colonies had a creamy appearance and a powdery surface. Irregularly shaped and sized macroconidia with three to nine septa, pear-shaped or more elongated microconidia attached at right-angles along the sides of hyphae and numerous coiled spirals were observed microscopically, allowing the identification of *Trichophyton mentagrophytes*. This diagnosis was confirmed by sequencing, using fungus-specific universal primers to amplify the ITS1 region [ITS1 (5′-TCCGTAGGTGAACC TGCGG-3′); ITS2 (5′-GCTGCGTTCTTCATCGATGC-3′)]1. The PCR product was then sequenced in an ABI-PRISM3100 (Applied Biosystems, Foster City, CA, USA). One sequence of 330 bp was obtained and compared against the CBS database (http://www.cbs.knaw.nl/collections/BioloMICSSequences.aspx?file=all), confirming the diagnosis of *Trichophyton mentagrophytes* (var. *erinacei*) infection (99.05% of identities with the best-match sequence–accession number 677.86).

Although data regarding epidemiology and therapy were lacking for fennec foxes, a fair prognosis was given and therapy was started, based on recommendations for dogs, i.e. combining systemic and topical treatments. Itraconazole was given orally at 5 mg/kg once daily (Itrafungol; Lilly France SA, Suresnes, France) for 6 weeks. A miconazole and chlorhexidine shampoo (Malaseb shampoo; Dechra Veterinary Products SAS, Suresnes, France) was applied on affected areas once weekly, followed by an enilconazole dip (Imaveral; Lilly France SA, Suresnes, France).

A good clinical improvement, with evidence of hair regrowth, was obtained. A fungal culture performed at 6 weeks was negative. Fungal medication was then stopped. Unfortunately, a few days later, the fennec fox developed anorexia and jaundice. Liver failure was confirmed on the biochemistry profile by elevation of alanine aminotransferase (>1000 UI/L; reference range
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Figure 4. Second set of skin biopsies. High-power photomicrograph showing high numbers of arthrospores and fungal hyphae in the stratum corneum; periodic acid Schiff stain.

35–162 UI/L, alkaline phosphatase (2040 UI/L; reference range 16–142 UI/L) and total bilirubin (221 μmol/L; reference range 1.7–5.1 μmol/L). Despite intravenous fluid infusion, the fennec fox deteriorated and died. The body could not be obtained for postmortem examination.

Discussion

This case illustrates the challenging diagnosis of Trichophyton dermatophytosis and the difficulty in selecting therapeutic protocols for exotic animals due to lack of data. Mycological culture remains the most reliable technique for confirming dermatophytosis.

In this case, the carpet square method proved ineffective on its own to collect fungal spores, which were located in the superficial layers of the stratum corneum but not widespread in the haircoat. It would have been preferable to collect crusts and scales, which might have increased fungal culture sensitivity. Moreover, the histopathological examination failed to show arthrospores or hyphae in the samples, even after careful re-examination of the slides once a definitive diagnosis had been established.

Although histopathological examination is less sensitive than fungal culture, most of the time this technique is efficient and useful to reveal fungal infection. In Trichophyton infection, fungal arthrospores and hyphae are often difficult to observe and far less numerous than in Microsporum canis infection.

Alternatively, the very few fungal elements contained in the most superficial layers of the skin (crusts and scales) could have detached during formalin fixation.

The first biopsy series showed an interface dermatitis pattern on histopathological examination. This particular presentation without observation of fungal elements introduced confusion. The histopathological features of dermatophytosis commonly consist of suppurrative luminal folliculitis, sometimes associated with furunculosis. Much less frequently, acantholysis can be associated with dermatophytosis, which both clinically and histologically resembles superficial pemphigus. This has been mainly reported with Trichophyton spp. and Microsporum persicolor, which preferentially colonize the epidermal surface keratin. Acantholysis is ascribed to keratinases and other proteolytic enzymes produced by the fungi. Acantholytic keratinocytes were observed on the initial cytological examination, most probably caused by the concurrent bacterial infection, but acantholysis was not confirmed on histopathology. In very few cases, dermatophytosis shows as an interface-like dermatitis, with an inflammatory reaction restricted to the superficial dermis and the follicular wall. In dogs, a case series of Trichophyton infections was described, and in all four cases, histopathological findings suggested an immune-mediated disease and more specifically, pemphigus erythematosus, combining an acantholytic intraepidermal pustular dermatitis and a severe epidermal and follicular interface dermatitis. More recently, in a retrospective study of 16 cases of dermatophytosis due to M. persicolor, a lichenoid interface dermatitis was present in all 10 cases that were biopsied. This pattern seems to be more common in Trichophyton and in M. persicolor (formerly named Trichophyton persicolor) infections. Trichophyton spp. could be less adapted to the host and hence induce a more intense cell-mediated immune response than the better adapted M. canis.

Dermatophytes are usually identified on the basis of macroscopic and microscopic characteristics of fungal colonies obtained on specific media. Molecular biology techniques, such as RT-PCR, can be used successfully with high specificity and sensitivity. Nevertheless, this method remains a research tool. The PCR test requires a preliminary fungal culture and isolation of dermatophytes from the very numerous contaminants found in pets and wild animals. In a previous study, PCR test permitted the distinction between two different species of T. mentagrophytes complex: Arthroderma benhamiae and Arthroderma vanbreuseghemi. The first type seemed to be more common in guinea pigs and the second type in cats and dogs with outdoor living conditions in rural areas. In the present case, the PCR test did not permit the distinction between the two species. Nevertheless, the macroscopic and microscopic features were most consistent with A. benhamiae.

No bibliographic data are available concerning treatment of dermatophytosis in the fennec fox. Systemic itraconazole in a liquid form seemed to be most appropriate, considering its greater safety than ketoconazole and its ease of administration. With regard to the topical therapy, the skin was carefully dried after each application to minimize stress, hypothermia and possible oral intake. Itraconazole is believed to carry a lower risk of hepatic toxicity than ketoconazole. In humans, hepatic failure caused by itraconazole is very rare. Acute liver failure due to itraconazole is not reported in dogs. Post-mortem examination could not be performed, leaving uncertainty about itraconazole toxicity causative of the death of the fennec fox. To the best of our knowledge, in addition to being the first report of dermatophytosis in a fennec fox, although a complete postmortem examination could not be performed, this is possibly the first report of fatal acute liver failure caused by itraconazole in a canid species.

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Trichophyton in a fennec fox

Résumé

Un renard fennec mâle de 2 ans présente des lésions cutanées crouteuses, non prurigineuses sur la tête, les pavillons auriculaires et l’extrémité de la queue. Les premiers examens comprenant une hématologie de routine, un profil biochimique, de multiples raclages cutanés, un trichogramme, un examen à la lampe de Wood et une culture fongique n’ont révélé aucune anomalie. Un examen histopathologique d’une première série de biopsies cutanées a montré une dermatite d’interface, un infiltrat lymphocytaire de la couche basale, une exocytose lymphocytaire significative et d’occas Ionnels kératinocytes apoptotiques épidermiques basaux; une coloration à l’acide périodique de Schiff n’a révélé aucun élément fongique. Des biopsies supplémentaires, on observait une dermatite pustuleuse neutrophilique avec de nombreuses croutes contenant un grand nombre d’arthrospores et d’hyphes fongiques. La culture fongique et une PCR ont permis de confrimer une infection à Trichophyton mentagrophytes.

Resumen

Un fennec macho de 2 años se presentó con una historia de 4 meses de lesiones cutáneas cróptas, no pruriginosas de la piel y con costras en la frente, los pabellones auriculares y la extremidad de la cola. Las investigaciones iniciales, incluyendo hematología rutinaria, perfil de bioquímica sanguínea, raspados múltiples de la piel, examen tricóscopico, examen con lámpara de Wood y cultivo de hongos no revelaron ninguna anormalidad. El examen histopatológico de una primera toma de biopsias de la piel demostró un patrón de dermatitis de interface, con infiltración de linfocitos en el estrato basal de la epidermis, exocitosis importante de linfocitos y algunos queratinocitos basales en apoptosis; la tinción ácida periódica de Schiff no desveló la presencia de hongos. En nuevas biopsias se observó una dermatitis neutrofílica con pustulas, y en las costras había un elevado número de arthrosporas y de hifas de hongos. Se confirmó una infección por Trichophyton mentagrophytes mediante cultivo y PCR. El fennec recibió itraconazol oral (5 mg/kg una vez al día durante 6 semanas) combinado con un champú de miconazol y de cloralhexidina aplicado en áreas afectadas una vez a la semana, seguido de una inmersión en enilconazol. El animal mejoró dramaticamente, y un cultivo de hongos realizado a las 6 semanas fue negativo. Desafortunadamente, algunos días después el fennec desarrolló anorexia, icterus y murió al poco tiempo.

References

A nuestro entender este es el primer informe de infección por *Trichophyton* en un fenec y aunque la autopsia no fue realizada, éste posiblemente sea el primer caso de fallo hepático agudo asociado con el tratamiento con itraconazol en un cánido.

**Zusammenfassung**

Ein 2-Jahre alter männlicher Wüstenfuchs wurde mit der Anamnese einer bereits 4 Monate andauernden Erkrankung vorgestellt, die sich in Form von juckenden, krustigen Hautveränderungen an der Stirn, an den Pinnae und an der Schwanzspitze äußerte.


**要約**

2歳齢の雄のフェネックギツネが、4ヶ月前から顔、耳、尾の先に非そう痒性の発疹を伴う皮膚病変を示すということで来院した。

一般血液検査と生化学検査ならびに被検部位からの皮膚搔爬検査、被毛検査などの初期検査を行った。ウィンド灯検査と真菌培養では異常所見はなかった。最初の皮膚生検による病理組織学的な検査では、表皮側のリンパ球浸潤、リンパ球の表皮内細胞浸潤、ときに基底膜側の表皮ケラチノサイトのアポトーシスを伴う境界部皮膚炎が認められた；過塩素酸シフ染色では真菌成分は認められなかった。さらなる生検にて、多数の被着胞子と菌糸を含む複数の発疹を伴う鮮血性好中球性皮膚炎が認められた。

*Trichophyton mentagrophytes*感染が真菌培養とPCRにて確認された。

フェネックギツネにはイトラコナゾール（5 mg/kg 1日1回6週間）を経口投与し、ミクナゾール、クロルヘキサンジン配合シャンプーで患部をシャンプーした後に、エニルコナゾールへの浸漬を1回行った。

症状は劇的に改善し、6週間後に実施した真菌培養は陰性であった。不運なことに、数日後にフェネックの食欲が減退、黄疸が認められ亡くなった。

筆者の知るところにおいて、これはフェネックギツネでの*Trichophyton*感染症の最初の報告で、剖検は行われなかったが、イヌ科動物でのイトラコナゾールによる、最初の致死的な急性肝不全の報告である可能性がある。

**摘要**

2只2歳雄性非洲狐有四个月的皮肤疾病，无瘙痒，前额、耳廓和尾尖可见结节性皮肤病变。

最初的调查研究，包括常规的血液生化、全面生化检查、多尿皮肤病变、毛发形态检查、焦油染料检查和真菌培养，未发现任何异常情况。首次的一套皮肤活检样本，显示界面性皮炎模式，基底层伴有淋巴细胞浸润，显著的淋巴细胞浸润和偶见基底表皮角质形成细胞的坏死。高硫酸希夫染色未发现真菌的存在。之后的活检可见脓疱性中性粒细胞皮炎，很多细胞含有大量分生子和菌丝。真菌培养和PCR确定为须毛癣菌感染。

这只非洲狐服用伊曲康唑（5 mg/kg，每天一次，持续6周），并被用碘化钾和氯已定香波每周一次清洗患处，随后使用思康唑浸润。皮肤改善显著，在6周时进行真菌培养，结果阴性。不幸的是，几天后这只非洲狐出现厌食、黄疸并死亡。

作者所知，这是首例非洲狐假毛癣菌感染的报道，尽管未进行尸体解剖，这可能是首例与伊曲康唑有关的犬科动物肝功能衰竭导致的死亡的报道。