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Comments on Case Report

A fatal case of *Aspergillus felis* infection in an immunocompetent host

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Comments on Case Report: A fatal case of *Aspergillus felis* infection in an immunocompetent host

Vanessa R. Barrs*

I read with sadness the report of an immunocompetent 18-year-old man with fatal fungal rhinosinusitis (FRS) and cerebral abscess caused by *Aspergillus felis*.

The parallels between this case and infections reported in immunocompetent domestic cats are striking. *A. felis* was described a decade ago after its isolation from pet cats in Australia with invasive fungal rhinosinusitis (FRS) characterized by sinonasal and sino-orbital involvement [1, 2]. As in this human case report, cats usually succumb once there is central nervous system (CNS) involvement, despite aggressive treatment with targeted antifungals [3].

A. felis is an environmental saprophyte that has been isolated from diverse environments on most continents [4]. Parkes-Smith *et al.* state that there are six pathogenic species within the *Aspergillus viridinutans* complex: *A. udagawae*, *A. felis*, *A. pseudofelis*, *A. parafelis*, *A. pseudoviridinutans* and *A. wyomingensis*. However, the complex has undergone extensive revision after sequencing of clinical and environmental strains from six continents [5]. It is now recognized that *A. felis*, *A. parafelis* and *A. pseudofelis* are, in fact, one species (*A. felis*). Ten species make up the *A. viridinutans* complex, two of which have only been isolated from Australia – *A. viridinutans* [6] and *A. frankstonensis* [7]. The former was isolated from rabbit dung in Frankston in 1954, and the latter from soil and air by former PhD student in my laboratory, Dr Jess Talbot, after we drove to Frankston, on a whim in 2015, to do some environmental sampling during the ISHAM Congress in Melbourne.

I have wondered why it is that apparently immunocompetent cats develop invasive FRS. Over-representation of Persian-related cat breeds raises the possibility of an uncharacterized genetic defect in fungal immunity or of impaired sinus drainage due to foreshortening of the skull (brachycephaly). In favour of the former, these same breeds of cats are also susceptible to other invasive fungal infections (IFIs), such as dermatophytic pseudomycetoma. There has been very limited veterinary research to investigate putative immunological defects. The findings from one study did not support a role for single-nucleotide polymorphisms (SNPs) in the coding regions of pattern recognition receptor genes, specifically Toll-like receptor (TLR) genes 1, 2 and 4, in the pathogenesis of fungal rhinosinusitis caused by *Aspergillus* species in cats [8].

Regardless, invasive FRS also occurs in immunocompetent crossbred cats with no known underlying risk factors. An analogous condition, that of chronic granulomatous invasive fungal sinusitis, caused by *Aspergillus flavus*, has been reported for decades in immunocompetent or mildly immunosuppressed people from Sudan, India, Pakistan and Saudi Arabia [9]. The environmental burdens of *A. flavus* conidia are high in these regions [10]. Exposure to high environmental spore burdens may be the most logical explanation for the development of invasive FRS in some immunocompetent cats.

A role for species-specific fungal virulence factors in the development of invasive FRS in immunocompetent individuals must also be considered. In experimental models the *A. felis* type strain (isolated from a cat with sino-orbital aspergillosis) showed significantly higher virulence in *Galleria mellonella* larvae than *Aspergillus fumigatus*. In immunosuppressed BALB/c mice, *A. felis* showed slightly higher virulence than *A. fumigatus*. However, in a chronic granulomatous disease murine model, inoculation with *A. fumigatus*, unlike *A. felis*, was uniformly fatal, demonstrating decreased virulence in hosts deficient in production of reactive oxygen species [11]. Another study investigated changes on computed tomography of the head in immunocompetent cats with invasive and non-invasive FRS caused by any *Aspergillus* species, where the infecting isolate had been identified by PCR and sequencing of the internal transcribed spacer (ITS) regions (ITS1–5.8S–ITS2), partial β -tubulin and/or partial calmodulin genes [12]. There was a strong association between the infecting species and anatomical site of aspergillosis, with infections caused by *A. fumigatus* confined to the sino-nasal cavity, while cryptic species infections (mostly caused by *A. felis*

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Keywords: *Aspergillus viridinutans* complex; veterinary mycology; aspergillosis.

Abbreviations: CNS, central nervous system; FRS, feline fungal rhinosinusitis; ISHAM, International Society of Human and Animal Mycoses; ITS, internal transcribed spacer; MEC, minimum effective concentration; MIC, minimum inhibitory concentration; SNP, single nucleotide polymorphism; TLR, toll-like receptor.

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and *A. udagawae*) were associated with invasive sino-orbital disease, including orbital and paranasal soft tissue involvement and lysis of the orbital bone.

A further consideration is that *A. viridinutans* complex members are heterothallic but, unlike *A. fumigatus*, readily produce teleomorphs [5]. Whether there is any difference in the ability of asexual (conidia) or larger sexual spores (ascospores) to induce invasive infections, and the comparative localization of these inhaled bioaerosols, has not been investigated.

The antifungal susceptibility profile of the *A. felis* isolate reported by Parkes-Smith *et al.* is typical of most *A. viridinutans* complex members, i.e. low MICs/MECs of posaconazole and echinocandins, respectively, elevated MICs of voriconazole and itraconazole and variable MICs of amphotericin B. The combination of posaconazole and liposomal amphotericin B used in the report was also used to cure a cat with FRS caused by *A. felis* [1]. More recently, two cats with sino-orbital aspergillosis caused by *A. udagawae* and *A. felis* were cured with combined therapy including posaconazole, caspofungin and terbinafine and remained asymptomatic more than 2 years after presentation [13]. A human patient with X-linked chronic granulomatous disease who developed severe vertebral osteomyelitis caused by *A. udagawae* was treated successfully using posaconazole and caspofungin [14].

Finally, a shout-out to the One Health approach of Australian microbiologists and to the International Society of Human and Animal Mycoses (ISHAM), where sharing of comparative human and animal data has long been actively encouraged. Together, we can learn more.

Funding Information

The author received no specific grant from any funding agency.

Conflicts of interest

The author declares that there are no conflicts of interest.

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Peer review history

VERSION 2

Editor recommendation and comments

<https://doi.org/10.1099/acmi.0.000561.v2.3>

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Lindsey Tolman; University at Albany, UNITED STATES

Date report received: 07 March 2023

Recommendation: Accept

Comments: This is a study that would be of interest to the field and community. All reviewer comments have been adequately addressed.

SciScore report

<https://doi.org/10.1099/acmi.0.000561.v2.1>

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iThenticate report

<https://doi.org/10.1099/acmi.0.000561.v2.2>

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Author response to reviewers to Version 1

Response Letter

Manuscript number: ACMI-D-22-00224

Thanks to the editor and reviewer for taking the time to review this letter and for your constructive suggestions. The reviewer concerns are addressed point by point below

Editor

Please provide a funding statement in the main manuscript under the heading 'Funding information'. If no specific funding was provided please include the line 'This work received no specific grant from any funding agency'.

Response:The requested information has been added.

Reviewers' comments and responses to custom questions:

Reviewer 1:

Please rate the quality of the presentation and structure of the manuscript

Reviewer 1: Good

Do you have any concerns of possible image manipulation, plagiarism or any other unethical practices?

Reviewer 1: No:

Reviewer 1 Comments to Author: The author has written this letter as a follow-up on the recent case published by Parkes-Smith et al related to fatal *Aspergillus felis* rhinocerebral infection in an immunocompetent patient. The author provides inputs related to this fungal infection from a veterinary standpoint and draws on her prior published research to highlight certain points.

Overall, the brief comments raised by the author provide interesting parallels between human and veterinary infections, as well as unique insights into this rare fungal infection. I have just a few comments as below.

Major Comments:

The author highlighted an interesting point that immunocompetent cats (particularly those of Persian-related breeds) may be predisposed to invasive fungal rhinosinusitis due to uncharacterized genetic defects or skull changes. Has there been any specific research related to this in veterinary medicine? It would be helpful to reference those studies. There have been limited studies in humans that have looked at the correlation between sinus cavity sizes and the occurrence of fungal balls (Michel et al DOI: 10.1111/coa.12813).

Response: Thank you for raising this point. There has been only limited research in veterinary medicine. One investigation looked at changes on computed tomography of the head in immunocompetent cats with invasive and non-invasive fungal rhinosinusitis caused by any *Aspergillus* species, where the infecting isolate had been identified by PCR and sequencing of the internal transcribed spacer (ITS) regions (ITS1–5.8S-ITS2), partial β -tubulin and/or partial calmodulin genes (1). There was a strong association between the infecting species and anatomic site of aspergillosis with infections caused by *A. fumigatus* confined to the sino-nasal cavity, while cryptic species infections (mostly caused by *A. felis* and *A. udagawae*) were associated with invasive sino-orbital disease including orbital and paranasal soft-tissue involvement and lysis of the orbital bone.

Findings from another study did not support a role for single nucleotide polymorphisms (SNPs) in the coding regions of pattern recognition receptor genes, specifically Toll-like receptor (TLR) genes 1, 2 and 4 in the pathogenesis of fungal rhinosinusitis caused by *Aspergillus* species in cats (2). This information and references have been added to the manuscript.

Minor Comments:

The author reports that *Aspergillus viridinutans* was isolated from rabbit feces in Frankston in 1954. It would be helpful to reference the study that this was reported in.

Response: Thank you for the suggestion – the reference has been added.

Please rate the quality of the presentation and structure of the manuscript

Reviewer 2: Very good

Do you have any concerns of possible image manipulation, plagiarism or any other unethical practices?

Reviewer 2: No:

Reviewer 2 Comments to Author: This short letter is a comment to a previously published case report (Case report: a fatal case of *Aspergillus felis* infection in an immunocompetent host, Access Microbiology, Volume 4, Issue 11), describing an unfortunate 18-year old succumbed from *A. felis* infection.

The manuscript was well written and statements were backed by citations, bringing up a few important key points about *A. felis* and its pathogenesis in humans and cats. *A. felis* was first described in 2013 and there are few published results on this pathogen. The author proposed that this pathogen needs more attention from microbiology and clinical fellows to share more data, to unveil pathogenesis mechanisms, and to demonstrate whether certain breeds of cats are more susceptible to *A. felis* infections.

Echoing the shout-out of the author of this letter, epidemiological investigation is recommended to be performed to identify where this patient got infected since he only has a healthy dog, whether there are any other individuals also got infected with possibly milder symptoms. Since this pathogen was recently identified and our understanding is poor, a better animal model mimicking infections would help obtain more knowledge on this pathogen and its related members.

Response: Thank you for the constructive comments.

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2. Whitney J, Haase B, Beatty J, Barrs VR. Genetic polymorphisms in toll-like receptors 1, 2, and 4 in feline upper respiratory tract aspergillosis. Vet Immunol Immunopathol. 2019;217:109921.

VERSION 1

Editor recommendation and comments

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Lindsey Tolman; University at Albany, UNITED STATES

Date report received: 27 February 2023

Recommendation: Minor Amendment

Comments: This study would be a valuable contribution to the existing literature. The reviewers have highlighted minor concerns with the work presented. Please ensure that you address their comments.

Reviewer 2 recommendation and comments

<https://doi.org/10.1099/acmi.0.000561.v1.3>

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Anonymous.

Date report received: 17 January 2023

Recommendation: Minor Amendment

Comments: The author has written this letter as a follow-up on the recent case published by Parkes-Smith et al related to fatal *Aspergillus felis* rhinocerebral infection in an immunocompetent patient. The author provides inputs related to this fungal infection from a veterinary standpoint and draws on her prior published research to highlight certain points. Overall, the brief comments raised by the author provide interesting parallels between human and veterinary infections, as well as unique insights into this rare fungal infection. I have just a few comments as below. Major Comments: The author highlighted an interesting point that immunocompetent cats (particularly those of Persian-related breeds) may be predisposed to invasive fungal rhinosinusitis due to uncharacterized genetic defects or skull changes. Has there been any specific research related to this in veterinary medicine? It would be helpful to reference those studies. There have been limited studies in humans that have looked at the correlation between sinus cavity sizes and the occurrence of fungal balls (Michel et al DOI: 10.1111/coa.12813). Minor Comments: The author reports that *Aspergillus viridinutans* was isolated from rabbit feces in Frankston in 1954. It would be helpful to reference the study that this was reported in.

Please rate the quality of the presentation and structure of the manuscript

Good

Do you have any concerns of possible image manipulation, plagiarism or any other unethical practices?

No

Is there a potential financial or other conflict of interest between yourself and the author(s)?

No

Reviewer 1 recommendation and comments

<https://doi.org/10.1099/acmi.0.000561.v1.4>

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Binjie Xu; Kingmed, CHINA

<https://orcid.org/0000-0002-9652-7813>

Date report received: 26 February 2023

Recommendation: Accept

Comments: This short letter is a comment to a previously published case report (Case report: a fatal case of *Aspergillus felis* infection in an immunocompetent host, Access Microbiology, Volume 4, Issue 11), describing an unfortunate 18-year old succumbed from *A. felis* infection. The manuscript was well written and statements were backed by citations, bringing up a few important key points about *A. felis* and its pathogenesis in humans and cats. *A. felis* was first described in 2013 and there are few published results on this pathogen. The author proposed that this pathogen needs more attention from microbiology and clinical fellows to share more data, to unveil pathogenesis mechanisms, and to demonstrate whether certain breeds of cats are more susceptible to *A. felis* infections. Echoing the shout-out of the author of this letter, epidemiological investigation is recommended to be performed to identify where this patient got infected since he only has a healthy dog, whether there are any other individuals also got infected with possibly milder symptoms. Since this pathogen was recently identified and our understanding is poor, a better animal model mimicking infections would help obtain more knowledge on this pathogen and its related members.

Please rate the quality of the presentation and structure of the manuscript
Very good

Do you have any concerns of possible image manipulation, plagiarism or any other unethical practices?
No

Is there a potential financial or other conflict of interest between yourself and the author(s)?
No

SciScore report

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