CASE REPORT

Fatal disseminated toxoplasmosis in a feline immunodeficiency virus-positive cat receiving oclacitinib for feline atopic skin syndrome

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Abstract

Toxoplasma gondii is a ubiquitous protozoan, for which felids are the definitive host. Immunocompromised individuals are susceptible to recrudescent toxoplasmosis. This case describes a 6-year-old, feline immunodeficiency virus-positive domestic short hair cat with feline atopic skin syndrome that developed fatal toxoplasmosis after treatment with oclacitinib for five months.

INTRODUCTION

Feline atopic skin syndrome (FASS) is a cutaneous hypersensitivity to environmental allergens diagnosed on history, clinical signs and exclusion of other causes of pruritic dermatoses.[1] The management of feline pruritus can be challenging. Glucocorticoids and cyclosporin are commonly prescribed, although potential adverse effects can make their long-term use problematic. Oclacitinib (Apoquel, Zoetis; Parsippany-Troy Hills, NJ, USA) is a first-generation Janus kinase 1 (JAK1) inhibitor approved for control of canine atopic dermatitis. Oclacitinib has proven effective for treatment of FASS as a consequence of its anti-pruritogenic and anti-inflammatory properties.[2] Oclacitinib is not registered for use in cats, so all use is off-label.

Systemic toxoplasmosis has been reported in immunocompetent adult cats, cats receiving cyclosporin or prednisolone for FASS[3,4] and immunocompromised cats with feline immunodeficiency virus (FIV) or feline leukaemia virus.[5] The risks of using oclacitinib in immunosuppressed cats has not been evaluated.

CASE REPORT

A 6-year-old male neutered FIV-positive domestic short hair cat was referred for evaluation of pruritus of one year duration. The cat was acquired as an FIV-positive kitten from a shelter, ate a commercially available cooked and canned food (ZIWI Peak Venison, ZIWI Peak; Christchurch, New Zealand) and was housed indoors. Supervised, outdoor access was permitted within a courtyard using a leash. No hunting, scavenging or interaction with other animals were known to have occurred, and there was no known rodent exposure.

Physical examination revealed widespread, patchy alopecia affecting the medial antebrachia, pinnae, axillae and ventrum. The owner scored the cat as eight out of 10 on a Pruritus Visual Analog Scale (PVAS). Ectoparasites were not observed on skin scrapings or acetate tape preparations. Topical indoxacarb (Activyl, Merck; Darmstadt, Germany) was applied every four weeks for flea control. Exposure to other insects was assumed to be minimal owing to the cat being housed indoors. A strict elimination diet using a hydrolysed diet

(Feline Anallergenic, Royal Canin; Aimargues, France) was performed for 12 weeks with no reduction in pruritus. A cutaneous adverse food reaction therefore was excluded and a diagnosis of FASS made.

Intradermal testing and serological testing for allergen-specific IgE (Veterinary Allergy Reference Laboratory; VARL) identified sensitivity to environmental allergens. Following an induction rush protocol, allergen-specific immunotherapy was commenced using monthly maintenance injections of 1 mL of 20,000 PNU administered subcutaneously. Prednisolone (Redipred, Aspen Pharmacare Australia; St Leonards, NSW, Australia) was commenced (1 mg/kg orally, twice daily). Topical 0.584% hydrocortisone aceponate (Cortavance, Virbac; Carros, France) was applied to pruritic areas once daily for seven days, then twice weekly. Cetirizine (Zyrtec, Johnson & Johnson; New Brunswick, NJ, USA) (2 mg/kg p.o., once daily) was added after four weeks and the prednisolone dose was 1 mg/kg p.o., once daily.

After three months, the PVAS was unchanged with no improvement in lesions. Prednisolone was withdrawn and oclacitinib administered at a dose of 1 mg/kg p.o., twice daily. Cyclosporin was considered to be contraindicated for this cat as a result of its positive FIV status. Haematological and serum biochemical evaluations, urinalysis and urine culture were performed before and six weeks after the initiation of oclacitinib and revealed no significant abnormalities. At the six week review, hair regrowth was noted in all previously alopecic areas and the owner scored pruritus as a two of 10 on the PVAS.

Four months after commencing oclacitinib, the cat presented to the local veterinarian with a two week history of inappetence, vomiting and lethargy. Haematological and serum biochemical evaluation identified lymphopaenia, eosinopaenia, hypocalcaemia and hypophosphataemia. Abdominal ultrasound identified pancreatitis. Ondansetron (Zofran, GlaxoSmithKline; Brentford, UK) 1 mg/kg p.o., twice daily), omeprazole (Losec, AstraZeneca; Cambridge, UK) 1 mg/kg p.o. once daily) and mirtazapine (Apo-Mirtazapine, Apotex; Toronto, Canada) 0.75 mg/kg p.o., once daily) were prescribed. Two weeks later, the cat had recovered and re-presented to the dermatology clinic. Repeat haematological, serum biochemical and urinalysis tests were within reference intervals. Owner-scored pruritus was one out of 10 on the pVAS and the cat had no skin lesions. The oclacitinib dose was reduced to 0.72 mg/kg p.o., twice daily.

Four weeks later, the cat presented to the local veterinarian after the acute onset of expiratory dyspnoea, anorexia and lethargy. Haematological and serum biochemical evaluation revealed a marked nonregenerative anaemia, profound left-shift neutropaenia, eosinopaenia, hypokalaemia and hypocalcaemia. A mixed predominantly nodular pulmonary infiltrate (Figure 1) and hepatomegaly were identified on thoracic and abdominal radiographs. The cat was referred to an emergency centre where ultrasound-guided needle aspirates of lung and transtracheal wash identified tachyzoites consistent with
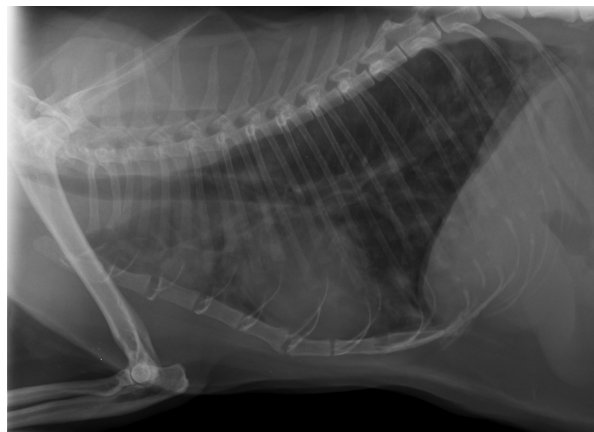
FIGURE 1 Lateral thoracic radiograph showing multiple nodular lesions with indistinct borders, consistent with pulmonary toxoplasmosis

Toxoplasma gondii infection. Immunoglobulin IgM and IgG toxoplasma antibody titres were <1:16 and 1:1,024, respectively. Intravenous trimethoprim sulfamethoxazole (30 mg/kg) and clindamycin (25 mg/kg), with oral pyrimethamine (1 mg/kg) were administered. Oxygen therapy was initiated yet the cat suffered cardiorespiratory arrest and died. Necropsy findings included white foci in the lungs and liver and yellow exudate in the caudal trachea (Figure 2). Histopathological examination and immunohistochemical (IHC) staining (Figures 3a–d and 4a, b) detected *T. gondii*. The diagnosis of disseminated toxoplasmosis was confirmed.

DISCUSSION

Oclacitinib is a JAK inhibitor that inhibits intracellular tyrosine kinases JAK1, JAK2, JAK3 and TYK2 involved in cytokine signalling.[2,6] Oclacitinib inhibits proinflammatory interleukins (IL)-2,4,6,13 and pruritogenic IL-31.[2,6] Oclacitinib causes *in vitro* immunosuppression in dogs via depletion of CD4+ and CD8+ T cells.[7] It seems probable that the same is true in the cat, even though few data are available on this topic.

It is suspected that five months of oclacitinib treatment, previous management with corticosteroids and co-infection with FIV resulted in immunocompromise, leading to recrudescent disseminated toxoplasmosis in this cat. A case of toxoplasma-associated retinitis has been reported in an immunocompromised adult male person receiving the JAK inhibitor ruxolitnib for myelofibrosis.[8]

Retroviral infections including FIV and human immunodeficiency virus (HIV) cause CD4+ T-lymphocyte cytopaenia and dysfunction.[4,5] HIV is a risk factor for toxoplasmosis in humans due to immunosuppression. Likewise, FIV-positive cats are predisposed to toxoplasmosis and other opportunistic infections, especially when receiving immunosuppressive drugs.[4] Recently, JAK inhibitors have been described to exhibit anti-viral activity through their ability to decrease the multiplication of virally infected cells in people with HIV, thereby inhibiting HIV latency reactivation through

T-lymphocyte suppression.[9] Such findings may support the prudent use of JAK inhibitors in FIV-positive cats, although more studies are needed. At present, there is no consensus regarding immunomodulatory treatment in immunocompromised cats.


FIGURE 2 Appearance of the caudal trachea, mainstem bronchi and lung at necropsy, demonstrating multifocal to coalescing round foci measuring 1–4 mm in diameter affecting the caudal left lung lobe

Histopathological and cytological identification of *T. gondii* in this case confirmed a diagnosis of disseminated toxoplasmosis. Bradyzoites were identified in the liver, adrenal glands and myocardium. Bradyzoites are usually quiescent until they are released from tissue cysts during recrudescence.[3,10] IHC revealed tachyzoites in the adrenal glands, liver, lung, brain and spinal cord. The detection of actively dividing tachyzoites suggests acute infection; however, with recrudescence, both multiplying and encysted forms of *T. gondii* can be present.[10] *Toxoplasma gondii* often is found in the pancreas in cats with acute systemic toxoplasmosis.[3] The pancreas was unaffected in this case at necropsy, with the cat's previous pancreatitis probably being unrelated. Recrudescence of latent disease is favoured in this case given the histopathological findings and the cat's strongly positive IgG titre.

The use of titre testing for definitive diagnosis of toxoplasmosis is problematic. It cannot be determined whether the cat was naïve or had recrudescence of latent infection as toxoplasma antibody titres were not performed before starting oclacitinib. At diagnosis, the cat's *T. gondii*-specific IgM titre was negative and *T. gondii*-specific IgG titre was positive. Cats with
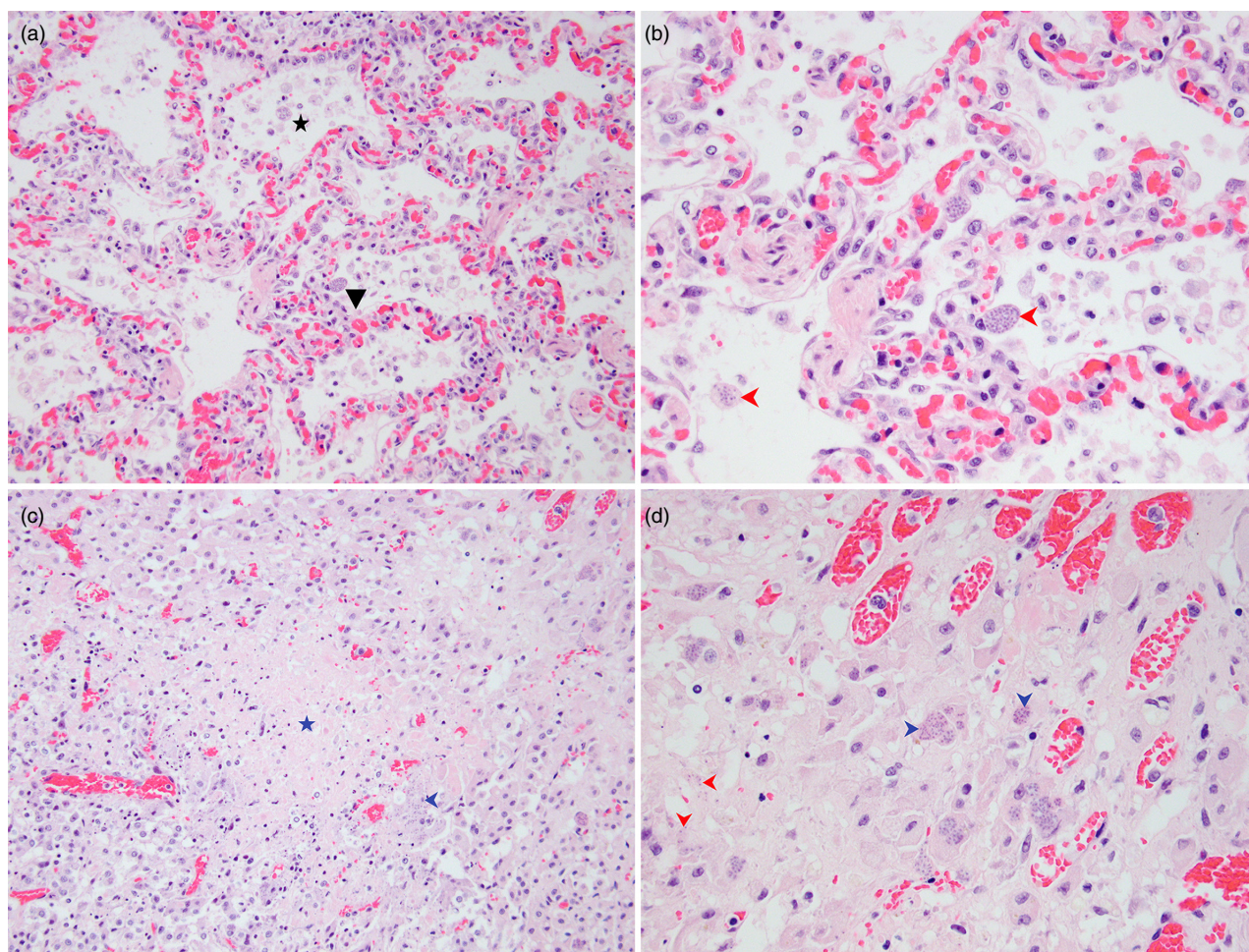
FIGURE 3 Histopathological results demonstrating *Toxoplasma gondii* in the lung and adrenal gland. (a) Lung: severe, multifocal to coalescing, acute, suppurative and histiocytic broncho-interstitial pneumonia. Alveolar macrophages within an alveolar lumen with intracytoplasmic tachyzoites (black star) consistent with *T. gondii*. Tachyzoites within an alveolar macrophage (black arrow.) (×200) (b) Lung: intracytoplasmic alveolar macrophages (red arrows; ×400) (c) Left adrenal gland: moderate, multifocal, adrenocortical necrosis with haemorrhage (blue star). Other changes include multiple pyknotic and karyorrhectic cells. At the edge of the lesion there are tachyzoites (blue arrow; ×200). (d) Left adrenal gland: bradyzoites (blue arrows) and tachyzoites (red arrows; ×400)
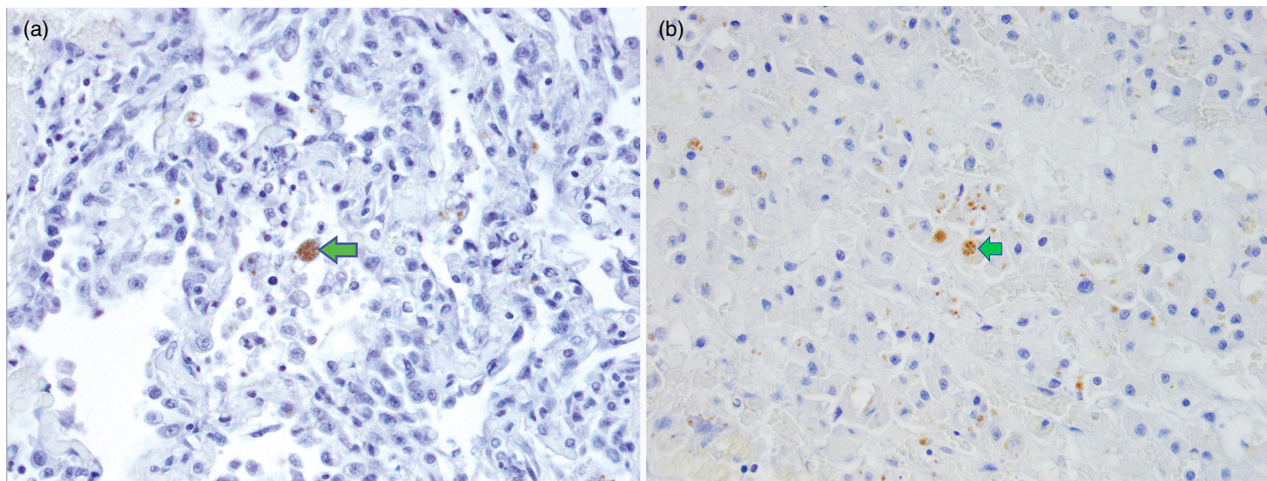
FIGURE 4 Representative immunohistochemical stains demonstrating tachyzoites (green arrows) in the lung (a, ×400) and adrenal gland (b, ×200)

experimental toxoplasma infection usually have detectable IgM within two to four weeks after inoculation which becomes negative by 16 weeks, and can remain positive in clinically ill cats, FIV-positive cats or cats with ocular toxoplasmosis.[10,11] However, positive IgM titres may never develop in approximately 20% of cats with toxoplasmosis, in cats with FIV and with glucocorticoid treatment.[11] As highlighted in this case, serology does not always correlate with the stage of infection.

A positive IgG titre reflects prior exposure and latent infection. IgG can be detected four weeks after infection and remains positive for years (likely lifelong) in exposed cats due to ongoing antigenic stimulation of bradyzoite cysts.[10,11] Thus, a positive IgG titre in a single serum sample cannot be relied upon to diagnose clinical disease.[10,11] Diagnosis of active infection is possible by performing two serum samples four weeks apart to demonstrate seroconversion via rising IgG levels.[3,10,11] In a clinical setting, this is rarely practical and most infections are diagnosed by visualising zoites in peritoneal and thoracic effusions, via histopathological examination or PCR.[10,11]

This is the first case of fatal disseminated toxoplasmosis associated with the use of oclacitinib in an FIV-positive, atopic cat. While oclacitinib offers a useful alternative for the management of FASS, we strongly recommend that clinicians avoid the use of raw meat diets and feed only cooked, commercial food owing to the potential risk of protozoal ingestion. Cats should be housed indoors to prevent hunting and scavenging, and to minimise rodent exposure. Haematological, serum biochemical and urinalysis testing is advised for monitoring changes in leucocyte numbers, renal dysfunction and other adverse effects.[2] Future studies are needed to evaluate the pharmacokinetics and long-term use of oclacitinib in cats.[12] A more controversial issue is whether clinicians should determine toxoplasma titres in cats before commencing oclacitinib, given that interpretation of antibody titres is unreliable. The use of oclacitinib for treatment of FASS in cats with concurrent retroviral infections should be approached with caution. Immunocompromise may lead to opportunistic infections; as such alternative anti-pruritic treatments should

be sought. Where no alternative exists, prophylactic use of clindamycin, pyrimethamine or trimethoprim sulfamethoxazole should be contemplated to mitigate the risk of disseminated toxoplasmosis following oclacitinib or cyclosporin treatment.[11]

AUTHOR CONTRIBUTIONS

Alexandra Moore: Conceptualisation, Investigation, Author of original draft, Data and information collection. **Amanda K. Burrows:** Conceptualisation, Investigation, Supervision, Writing-reviewing and editing. **Richard Malik:** Conceptualisation, Writing-reviewing and editing. **Rudayna M. Ghubash:** Writing-reviewing and editing. **Robert D. Last** and **Benjamin Remaj:** Investigation (pathology).

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CONFLICT OF INTEREST

There are no conflicts of interest to declare.

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Résumé

Toxoplasma gondii est un protozoaire ubiquitaire dont les félidés sont l'hôte définitif. Les personnes immuno-déprimées sont sensibles à la toxoplasmose recrudescente. Ce cas décrit un chat domestique à poils courts de 6 ans, positif pour le virus de l'immunodéficience féline, atteint du syndrome atopique cutané félin, qui a développé une toxoplasmose mortelle après un traitement à l'oclacitinib pendant cinq mois.

Resumen

Toxoplasma gondii es un protozoo ubicuo, cuyo huésped definitivo son los felinos. Las personas inmunocomprometidas son susceptibles a la toxoplasmosis recrudescente. Este caso describe un gato doméstico de pelo corto positivo para el virus de la inmunodeficiencia felina de 6 años de edad con síndrome de piel atópica felina, que desarrolló toxoplasmosis fatal después del tratamiento con oclacitinib durante cinco meses.

Zusammenfassung

Toxoplasma gondii ist ein ubiquitäres Protozoon, für welches Felidae den definitiven Wirt darstellen. Immunkompromitierte Individuen sind empfänglich für eine sich verschlimmernde Toxoplasmose. Dieser Fall beschreibt eine 6 Jahre alte Hauskatze, die auf das Feline Immunodefizienz Virus positiv getestet war und am felinen atopischen Hautsyndrom litt, welche nach einer 5 monatigen Behandlung mit Oclacitinib eine fatale Toxoplasmose entwickelte.

要約

Toxoplasma　gondiiは‚ネコ科動物を宿主とする至る所にある原虫である。免疫不全を起こしていると再発性トキソプラズマ症に罹患しやすい。本症例は、猫アトピー性皮膚症候群の猫免疫不全ウイルス陽性ドメスティック・ショート・ヘアー(6歳)が、オクラシチニブによる5カ月間の治療後に致死的なトキソプラズマ症を発症したものである。

摘要

弓形虫是一种普遍存在的原虫‚猫科动物是其终末宿主。免疫功能低下者易患复发性弓形虫病。该病例描述了1只患有猫特应性皮肤综合征的6岁家养短毛猫‚猫免疫缺陷病毒阳性‚在接受奥拉替尼治疗5个月后发生致死性弓形虫病。

Resumo

Toxoplasma gondii é um protozoário ubíquo para o qual os felídeos são o hospedeiro definitivo. Indivíduos imunocomprometidos são suscetíveis a toxoplasmose recrudescente. Este relato descreve um caso de um felino doméstico de pelo curto de seis anos de idade, positivo para o vírus da imunodeficiência felina, com síndrome atópica felina, que desenvolveu toxoplasmose fatal após tratamento com oclacitinib por cinco meses.