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Catastrophic Parasitic Meningoencephalitis Due to Halicephalobiasis: Case Report

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Authors' contributions

This work was carried out in collaboration with all authors. Author KFL wrote the detailed patient clinical record and the manuscript, conducted the review of literature, obtained consent from the patient's relative, provided and designed the figures. Authors KS and ML were involved with the provision of clinical material relevant to the case, critical appraisal and editing of the manuscript including submission and revision and offered intellectual input. Author LH was involved with background research and literature review and preparation of the manuscript. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Halicephalobus gingivalis is a free-living nematode and facultative parasite, rarely known to affect the central nervous system (CNS). We report the 6th case of Halicephalobiasis in humans worldwide and the first case of catastrophic meningoencephalitis caused by *Halicephalobus gingivalis* in Australasia, in a 73-year-old woman on long-term immunosuppressive drugs for rheumatoid arthritis. Her initial presentation and normal blood profile did not lead to a clinical suspicion of meningitis. A rapid deterioration in her neurological state to a GCS score of 6 was noted within 48 hours. Broad-

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spectrum antimicrobials and antivirals were commenced to treat possible severe meningoencephalitis, with the addition of an anti-helminthic therapy at a later stage. Due to medical futility and poor prognosis, multisystem organ supports were withdrawn and focus was changed to comfort care and she died on day 8 of admission. All human cases have reportedly led to death within ten days. Diagnosis through detection of parasites in the CSF is difficult as nematodes tend to be invasive and there is no immunoassay or polymerase chain reaction (PCR) test readily available. All cases have been diagnosed post-mortem and it is paramount that further research is conducted in this area of clinical parasitology for earlier detection and institution of therapy to achieve clinically meaningful outcomes.

Keywords: Halicephalobus gingivalis; neurohelminthiasis; parasitic meningoencephalitis; Disease-Modifying Antirheumatic Drugs (DMARDs); polymerase chain reaction.

1. INTRODUCTION

Helminthic infections and/or infestations of the central nervous system (CNS) are extremely rare and infrequent but should be considered in atypical presentations. *Halicephalobus gingivalis*, one of the nine species of the genus *Halicephalobus* is known to be capable of infecting vertebrates such as horses, zebras and humans. To the best of our knowledge, we describe the 6th human case of halicephalobiasis infection and the first in Australasia. Our patient was the oldest to date (73 year-old) and the first reported case involving an immunocompromised host. More recently, a news report of a triple fatality involving *H. gingivalis* following a kidney transplant to two recipients in the UK has been noted, increasing the number of known cases [1]. This has not been reported in literature. In contrast, equine cases of *H. gingivalis* have a wide geographical distribution, including America, Canada, United Kingdom, Switzerland, Iceland, Italy, Japan and Korea [2].

H. gingivalis is morphologically distinct compared to other types of nematodes: it has a typical rhabditiform oesophagus with corpus, isthmus and bulb [3]. Adult female worms characteristically have a dorsiflexed ovary, measuring approximately 250 to 460 micrometre (length) by 15 to 25 micrometre (diameter) [3]. A vulva with protruding lips divides the body into a 3:2 ratio; the anterior end tapers gradually to the stoma, and the posterior end tapers rapidly to the tail [4]. These roundworms have a thin cuticle with fine striations, but lack lateral or cuticular alae [5].

The life cycle, route of infection, and pathogenesis of *H. gingivalis* remains poorly understood. In equine, organs that are commonly affected include the brain, kidneys, lymph nodes, spinal cord, eyes, lungs, oral and nasal cavities, causing extensive granulomatous tissue lesions [2,6,7]. Clinical signs manifested in the horses are dependent on the organ involved, with predilection of the nematode to spread through the haematogenous route and infiltrate the CNS [2,6,7]. Subsequent signs that developed in the horses include ataxia, incoordination, depression, muscle spasms, abnormal behaviour and movements [2,6]. Horses which were found to have CNS involvement of *H. gingivalis* at necropsy exhibited rapid deterioration and invariably died. In humans, the postulated route of infection is likely through skin or oral mucosal laceration. Similarly, the nematode is hematogenously disseminated to CNS tissue causing extensive granulomatous inflammation in the brain parenchyma and meninges. Perivascular space distribution of the nematodes and eggs, some extending into the brain parenchyma is commonly observed in histopathological sections.

2. CASE PRESENTATION

A 73-year-old Caucasian woman presented to a regional hospital with a four day history of productive cough, fever, malaise, delirium and unsteady gait. She had no associated headache, neck stiffness, rash or visual disturbance. Past history included peripheral vascular disease necessitating great toe amputation and seropositive rheumatoid arthritis which had been stable and managed by methotrexate and etanercept for more than ten years. A provisional diagnosis of community acquired pneumonia was made and she was treated with intravenous piperacillin/tazobactam.

She kept pet cats and birds. She had visited a farm in Queensland ten months earlier where there was contact with healthy horses. She was an active smoker of 30 pack years. Physical examination was initially non-specific. Initial investigations showed profound hyponatremia, sodium 122 mmol/L, normal white cell count and

no eosinophilia. Imaging including tomography of the head chest abdomen and pelvis suggested collapse of the right lower lobe and a small posterior pleural effusion.

Rapid deterioration of her mental state by day 3 with a Glasgow coma scale of 6, necessitated endotracheal intubation, supportive mechanical ventilation and she was transferred to an intensive care unit of a tertiary referral center via air retrieval services. Differential diagnoses included septicemia, meningoencephalitis and central pontine myelinolysis. Antibiotics were upgraded to ceftriaxone, azithromycin, benzyl penicillin and acyclovir. Immunosuppressants were withdrawn.

She did not show signs of meningism and the Cerebro-spinal fluid (CSF) was cloudy and colorless on macroscopic examination. The opening pressure was not measured. CSF protein was high at 1.6 g/L with decreased glucose 3.3 mmol/L relative to serum glucose of 10 mmol/L. The CSF polymorph count was 280 cells/μL with mononuclear cells 18 cells/μL. There was a neutrophil predominance. CSF testing for bacteria, Cryptococcus, Acid Fast Bacilli, Enterovirus, HSV 1-2, VZV, BK and JC virus was negative. Serum sodium increased to 136 mmol/L by day 2 and the peripheral blood white cell count was mildly elevated.

Magnetic resonance imaging (MRI) of the brain was performed on day 2 which showed meningeal enhancement with raised T2 sub cortical white matter signal in the left fronto temporal lobe. Multiple punctate areas were demonstrated in sub cortical white matter at the vertex (Fig. 1). Given her clinical presentation, CSF findings, and MRI findings, we had a strong suspicion of meningoencephalitis. A stereotactic biopsy was contemplated at that stage, but after further discussion in the multidisciplinary meeting and considering the potential complications associated with the procedure, we opted to continue intravenous antimicrobials and to monitor her progress.

On day 5 she remained unresponsive despite 24 hours without sedation. There was a loss of brainstem reflexes, general hypotonia but the apnea test was negative. Lumbar puncture was repeated and showed CSF protein elevated to 5.5 g/L, glucose falling to 1.3 mmol/L and the polymorphonuclear cell count further elevated at 2500 cells/μL with mononuclear cells 34 cells/μL. The peripheral white cell count had risen to 22 x 10^9/L with neutrophil predominance and no eosinophilia. Antibiotics were modified to moxifloxacin, benzyl penicillin and acyclovir.

Microbiology remained negative but supplemental reports on day six suggested amoebic fragments in CSF. The latter prompted the addition of liposomal amphotericin B, pentamidine and sulphadiazine.

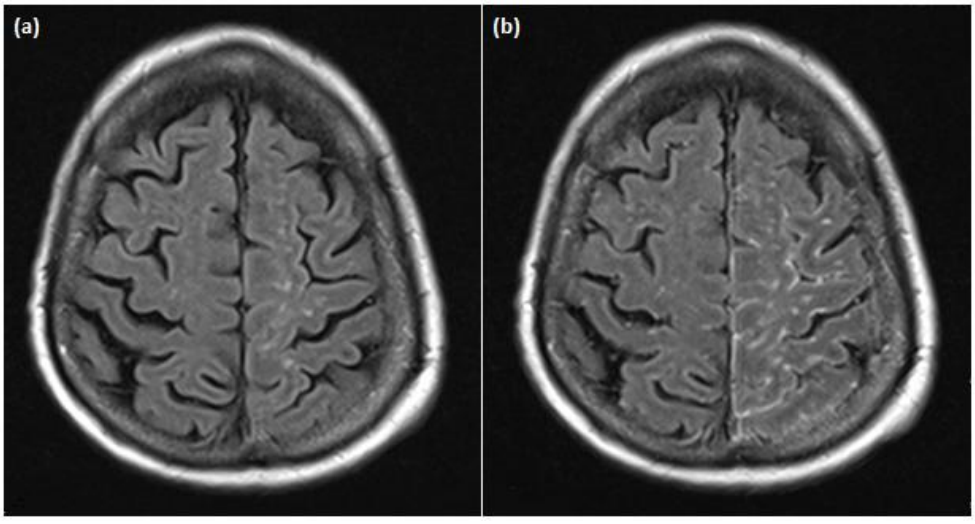

Fig. 1. Flair axial views (a) pre-contrast and (b) post-contrast: Magnetic resonance imaging (MRI) of the brain demonstrating meningeal enhancement and raised T2 subcortical white matter signal in the left fronto-parietal region towards the vertex and extending over the temporal lobes bilaterally

Methylprednisolone was initiated with the rationale of dampening the inflammatory reaction in the CNS.

On day 8 due to medical futility and poor prognosis, multisystem organ supports were withdrawn based on medical consensus with patient's family in agreement and comfort care was initiated, she died later that day.

At autopsy the external surface of the brain showed significant congestion of the leptomeningeal blood vessels predominantly seen over the fronto-parietal and temporal regions with cortical necrosis. CSF fluid was relatively clear without pus.

Microscopy showed necrotic panencephalitis predominantly affecting the temporal lobes, basal ganglia, anterior corpus callosum, right cerebral peduncle and cerebellum. A mononuclear inflammatory infiltrate accompanied by distribution of the nematodes and larvae in the perivascular spaces was evident in every section of brain (Figs. 2-5).

The CSF sample from brain dissection was sent to the Department of Veterinary Science at the University of Melbourne for further testing. Microscopic examination revealed the larvae and eggs of a helminth. PCR was performed to identify the specific neurohelminth species using molecular sequencing. The final nematode identification as *Halicephalobus gingivalis* was based on morphology and molecular PCR sequencing, yielding a 99% Gene Bank match.

Granulomatous inflammation was not seen. The degree of inflammation was relatively less than expected, given the severity of the widespread infection. There were no significant findings in extra neural tissue. We cannot confirm the possible infiltration of the nematodes in the spinal cord system as it was not dissected.

3. DISCUSSION

All five human cases of halicephalobiasis reported worldwide (one in Canada, four in USA), dating back to 1975, have featured lethal meningoencephalitis. This case was unique for the rapidity of the decline and severity of pathology, possibly ascribable to her immunosuppression and older age. The fever, CSF findings and MRI pointed to meningoencephalitis but she otherwise presented as a severe acute brain syndrome. Her survival to day 8 was largely due to supportive care but the situation appeared irretrievable as early as day 3.

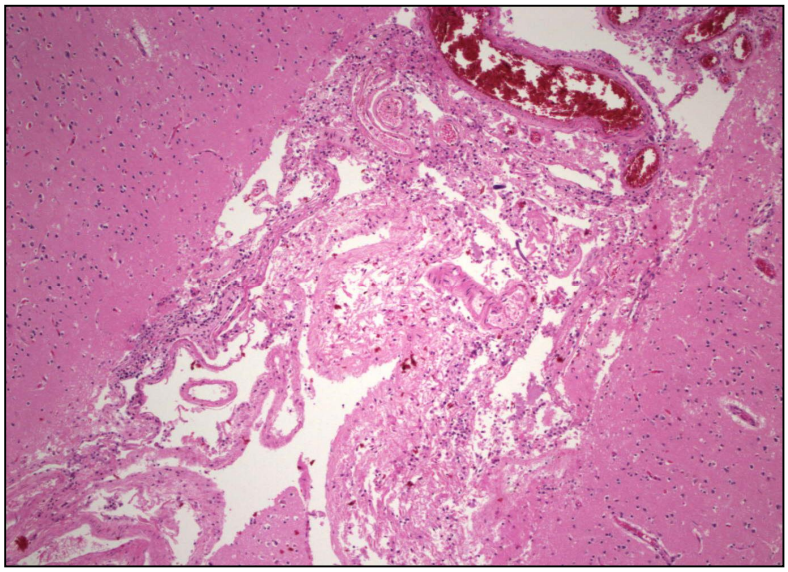

Fig. 2. A histology section of the leptomeninges showing microscopically congested vessels with marked inflammatory infiltrates (mainly macrophages and some lymphocytes). Nematodes are stained in a dark purple colour (centre)

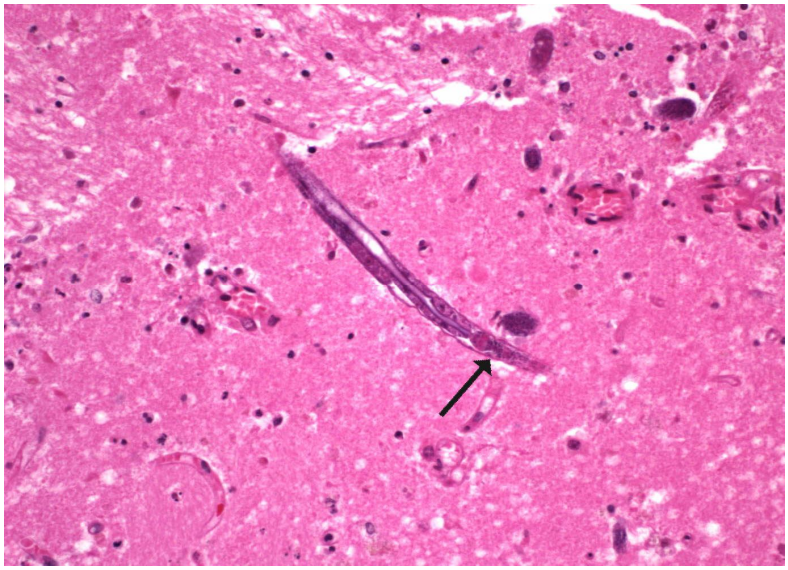

Fig. 3. Larvae of *H. gingivalis* with a characteristic rhabditiform oesophagus (two bulbous swelling- black arrow). The characteristic dorsiflexed ovary is absent which suggests that these are immature female worms

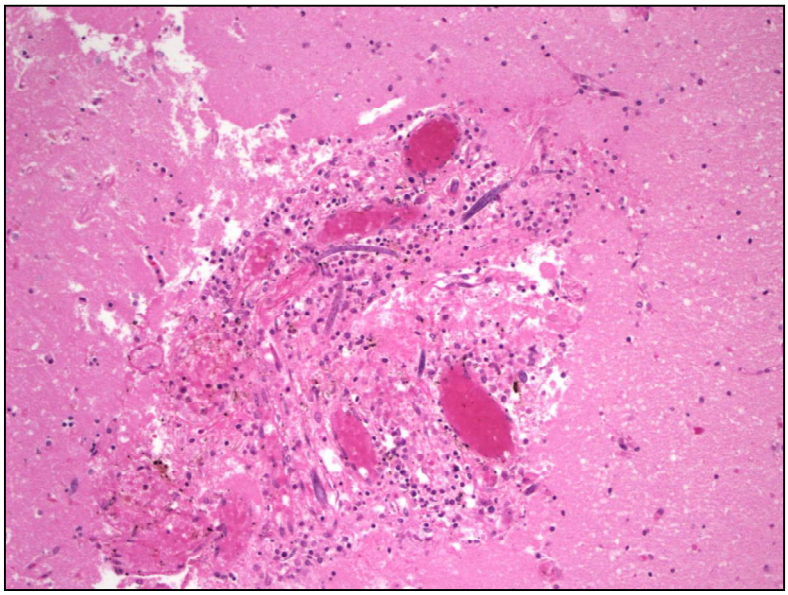

Fig. 4. Presence of larvae and eggs of *H. gingivalis and* associated inflammation in the perivascular spaces, extending into brain parenchyma

Her initial serum sodium level was profoundly low and difficult to interpret as a subsequent sodium level eight hours later was 131 mmol/L without any intervention and had normalised to 136 mmol/L on the following day. We were unable to rule out SIADH as urine and plasma osmolality were not tested at the regional hospital. Cerebral salt wasting syndrome was thought to be an unlikely diagnosis as she was euvolaemic on retrieval and did not display signs of autonomic dysfunction or polyuria. She was noted to be on long-term furosemide and had aggressive fluid resuscitation which suggests that the result could have been an artifact.

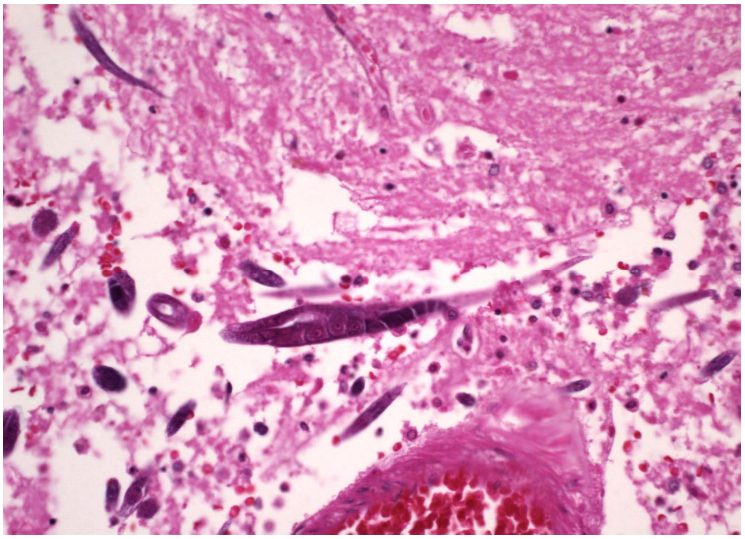

Fig. 5. Immature female nematode with eggs inside the ovary

Diagnosis through detection of parasites in the CSF is difficult as the nematodes tend to be invasive and there is no immunoassay or PCR test readily available. All cases have been diagnosed post-mortem. Cases could have been undiagnosed and unreported due to lack of post-mortem examination.

The pathogenesis and mode of transmission of *H. gingivalis* is not clearly understood. These free living saprophytic parasites are found in moist soil, decaying organic material, rotting plant matter, manure, fresh and salt water, and swampland environments. There was no obvious entry point in this patient and this was the case in half of the previous cases. However, it was noted that this patient had frequent pedal infections and eczema in the past. She often sustained superficial cuts on both hands from cooking and gardening.

Typical microscopic findings of the brain have been seen in all cases. These include extensive perivascular granulomatous inflammation and distribution of nematodes, oedema, focal haemorrhage, and necrosis. Given the perivascular distribution of these organisms, it is postulated that they spread to the CNS via the haematogenous route crossing the blood-brain barrier and replicate by parthenogenesis [8]. In one equine report, there was evidence of lymphatic spread as the organism was identified in lymph nodes [9].

This patient's first set of CSF results was undifferentiated and she was given standard treatment to cover bacterial or viral meningitis. The second CSF examination showed a rise in protein, mild eosinophilia and amoebic fragments, suggesting *that H. gingivalis* was possibly expressed in CSF and more sensitive testing may have revealed it. The positive CSF sample collected post-mortem could be explained by the contamination from brain tissue during dissection. This fits in with previous cases where the diagnosis of *H. gingivalis* was only revealed from microscopy, based on the typical morphological findings, prior to the availability of PCR testing. To date, only female nematodes of *H. gingivalis* have been isolated in all equine and human samples [10]. Interestingly, there were no adult worms seen in this case, unlike the typical findings in previous human and equine cases. Hence, we are unable to demonstrate the characteristic dorsiflexed ovary of the matured female nematode in the histopathological sections.

Differentials of nematode meningoencephalitis or meningoencephalomyelitis include *Strongyloides stercoralis, Angiostrongylus cantonensis, Toxocara* species, *Baylisascaris* species, and *Gnathostoma* species [3,5,8]. Other neurotropic nematodes are distinguished from *H. gingivalis* on the basis of unique morphological features in microscopy and genomic DNA in PCR. In our case, the neurohelminth species from the CSF sample submitted from autopsy was identified using microscopy that revealed the typical morphological features; and PCR molecular sequencing coupled with matching analysis using database of the isolated parasitic species from

the Gene Bank. We have no further information from the lab for detailed description of the PCR testing. In a recent fatal case of a horse infected by *H. gingivalis* reported by Jung JY et al. [2] the PCR technique used DNA extracted for molecular sequencing, followed by phylogenetic analysis based on the isolated species data from the Gene Bank. The use of common neurohelminthic species as comparison samples has been described for the purpose of parasitic species identification.

To date, no anthelminthic therapy is known to successfully target *H. gingivalis* in the human population. The speed of patient deterioration and the cryptic nature of infection may have precluded success. Treatment with ivermectin and benzimidazole has been administered on animals with *H. gingivalis* CNS infection but has been unsuccessful [11]. Possible explanations for this could be the inability of the anthelminthic drugs to penetrate the blood-brain barrier, or the insensitivity of *H. gingivalis* to these treatments. Only two successful equine cases treated with ivermectin and diethylcarbamazine have been reported which did not involve the CNS [8,12].

Anthelminthic treatments are not routinely considered due to their toxic side effects, the possibility of exacerbating CNS inflammation due to the death of the larvae and worms in the CNS, and insufficient clinical evidence of efficacy [13].

The role of immunosuppression in *H. gingivalis* has not been previously studied, as this is the first reported case of an immunocompromised host. The speed of the disease and the fatal outcome was the quickest of the cases reported to date. The recent report of two kidney transplant recipients who died of the fatal disease suggests that immunosuppression plays a part [1], although we have no further details on the clinical findings of those cases. Opportunistic parasitic CNS infections are not uncommon in immunocompromised hosts. Parasites may cause immediate symptoms or remain undetected for years once they have entered the human host. Marked inflammatory responses with extensive non-necrotising granulomatous lesions have been consistently seen in neuropathology evaluation of all cases, and this is believed to be induced by migrating or growing parasites. However, in the immunosuppressed patient, the inflammatory response and clinical manifestations may be masked. This patient, who was taking immunosuppressants for more than a decade, demonstrated a diffuse distribution of the nematodes in the brain and extensive necrosis of the brain parenchyma, but no granulomatous inflammation. The degree of inflammatory infiltrates was less than expected and a relatively clear CSF at autopsy for such an extensive and widespread infection by *Halicephalobus gingivalis*. Her serum eosinophilic count was not elevated throughout the course. Her previous complete blood counts were unremarkable with normal eosinophilic counts prior to this presentation. Her immunosuppressive state may have played a role in masking the hyper-eosinophilic pattern as evident in horses.

Etanercept is an established anti-TNF drug for rheumatological conditions. Whilst immunosuppression therapy is indicated as treatment for rheumatological conditions, it concomitantly increases the risk and severity of infection [13]. *Strongyloides sterocoralis* infection of the GI tract has been associated with the use of Etanercept [14]. Several cases of aseptic meningitis and drug-induced lymphocytic meningoencephalitis have also been reported [15].

4. CONCLUSION

Physicians should include Halicephalobiasis, a sporadic and lethal CNS infestation along with other neurotrophic parasites as a differential diagnoses for patients presenting with atypical meningoencephalitis. Unfortunately, screening tests for parasitic meningoencephalitis are lacking, with definitive diagnosis being delayed until autopsy. The efficacy of anthelminthic therapy has been uncertain, hence there is a need for intensive research in identifying rapid diagnostic tests and key therapeutic options in this life threatening disease.

CONSENT

Written informed consent was obtained from the deceased patient's next-of-kin for publication of this case report and accompanying images.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

All authors have declared that no competing interests exist.

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