Clinical Infectious Diseases

BRIEF REPORT

First Human Case of Metacestode Infection Caused by *Versteria* sp. in a Kidney Transplant Recipient

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Cestodes are emerging agents of severe opportunistic infections among immunocompromised patients. We describe the first case of human infection, with the recently-proposed genus *Versteria* causing an invasive, tumor-like hepatic infection with regional and distant extension in a 53-year-old female kidney transplant recipient from Atlantic Canada.

Keywords. metacestode infection; *Versteria*; kidney transplant recipient; immunosuppression; zoonosis.

A 53-year-old Caucasian female from rural New Brunswick (Atlantic Canada) presented to a community hospital in April 2017 with a 3-day history of fever, productive cough, myalgia, malaise, and anorexia. Her past medical history was remarkable for obstructive nephropathy necessitating a kidney transplant in 1992, for which she was on minimal immunosuppression with tacrolimus, mycophenolate mofetil, and prednisone (5 mg thrice weekly). Physical examination revealed a temperature of 40°C, oxygen saturation of 93% on 2L/min, hypotension, and tachycardia. The rest of the physical exam was noted as unremarkable. Laboratory findings on admission were notable for mild pancytopenia, decreased kidney function compared to baseline (estimated CrCl 22 mL/min), transaminitis (~8X normal), and elevated lactate dehydrogenase (Supplementary Table 1). A chest X-ray revealed bibasilar alveolar opacities as more prominent in the right lung. Empiric antibacterial therapy was initiated for presumed community-acquired pneumonia and the patient was transferred to a tertiary care centre for further evaluation.

Despite empiric meropenem, recurrent episodes of hypotension required vasopressors and repeated admissions to the intensive care unit. A chest computed tomography (CT) scan showed mixed alveolar ground glass opacities and a prominent right hilar lymph node (3.9 × 2 cm). Abdominal imaging revealed a large heterogeneous central hepatic lesion (19.3 × 15 × 8.7 cm) abutting the middle hepatic and left portal veins, with multiple satellite nodules (Figures 1 and 2). An abdominal CT scan performed 3 years earlier was unremarkable. Further tests—including a cerebral CT scan, a transesophageal echocardiogram, and a colonoscopy—revealed no other lesions. A laparoscopic liver biopsy revealed extensive necrosis, with focal necrotizing granulomas surrounding hooklets and a single protoscolex, consistent with a metacestode infection (Figure 3). Empiric treatment with albendazole for possible alveolar echinococcosis (AE) was initiated, and the patient was transferred to the J.D. MacLean Centre for Tropical Diseases in Montreal for further management.

Notable exposure history included living near a forest with her dog and with peridomestic wildlife such as foxes, coyotes, moose, deer, small rodents, and mustelids. She enjoys gardening and blueberry picking and drinks water from a surface well. She never traveled outside Canada, and noted a single 4-day trip to Edmonton (Canada) in 1980.

A whole-body positron emission tomography scan with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with CT (WB 18F-FDG PET/CT Scan) demonstrated low cervical, mediastinal, bilateral hilar, right axillary, and periportal adenopathy, as well as intense heterogeneous uptake of FDG in the liver. Histopathology of a biopsy of the right hilar lymph node performed by endobronchial ultrasound revealed granulomatous inflammation with extensive necrosis. Bacterial, mycobacterial, and fungal cultures were negative. The hepatic lesion was not considered resectable.

A screening enzyme-linked immunoassay (ELISA) using in-house crude antigens for *Echinococcus granulosus* was positive, with an optical density of 0.60 (cut-off value: 0.35). A second ELISA using an *E. granulosis* hydatid fluid antigen (EgHF) as previously described was also positive (156 AU/ml; cut-off ≥ 1 AU/ml) [1]. For *E. multilocularis*, 2 separate ELISAs, using (1) purified Em2 antigen (localized in the laminated layer) or (2) recombinant Em18 antigen (previously known as EmII/3-10-antigen, localized in the tegument of the protoscolex and the germinal layer) were negative [2, 3]. Confirmatory Western blots for *E. granulosus* and *E. multilocularis* were performed as previously described, and were negative as well [1, 4].

Needle biopsies of the liver were repeated and sent for molecular testing at the University of Bern, Switzerland. Deoxyribonucleic acid (DNA) was extracted from a fresh-frozen native biopsy

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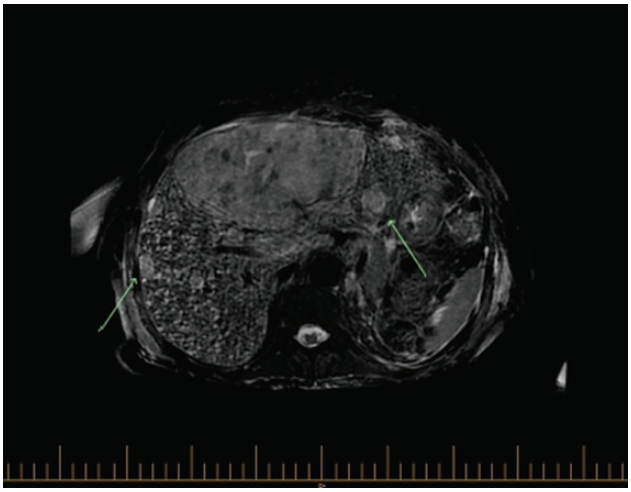

Figure 1. Axial T2-weighted magnetic resonance imaging scan of the liver, showing a large lesion occupying segments 3 and 4, with multiple satellite lesions (arrows), before initiation of albendazole and praziquantel.

specimen using a commercial kit, according to the manufacturer's instructions (QiAmp DNA mini kit, Qiagen, Hilden, Germany). In addition, DNA was also prepared from formalin-fixed paraffin-embedded liver tissue, as described by Müller et al. [5]. Multiplex polymerase chain reaction (PCR) targeting mitochondrial 12S rDNA for discrimination between different cestodes was performed as previously described [6]. *E. granulosus* and *E. multilocularis* can be identified directly, based on the size of their PCR product. A 264 base pair (bp) fragment was amplified from both fresh-frozen and paraffin-embedded specimens, corresponding to neither *E. granulosus* nor *E. multilocularis*. DNA sequencing of the PCR product was thus performed to identify the cestode.

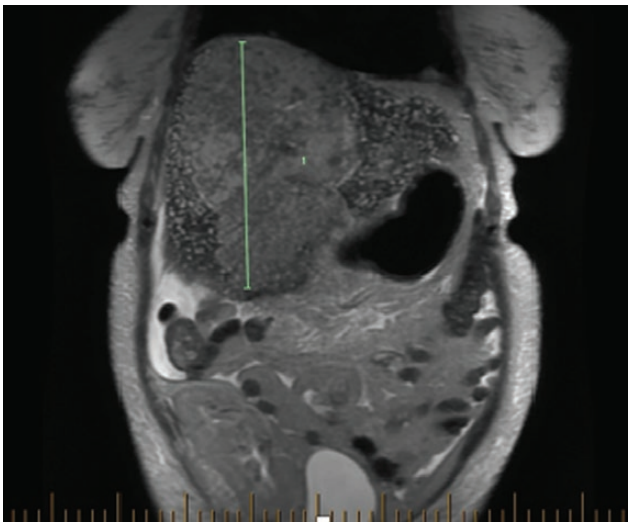

Figure 2. Coronal T2-weighted magnetic resonance imaging scan of the liver, showing a large lesion occupying segments 3 and 4, with multiple satellite lesions, before initiation of albendazole and praziquantel

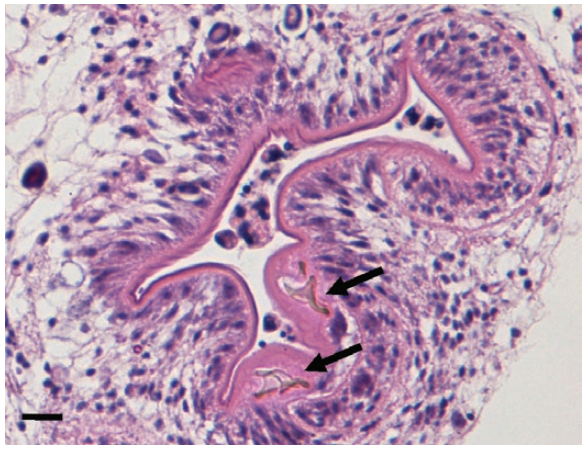

Figure 3. Hematoxylin and eosin staining of histopathology section, showing partial section through the parasite larvae with parts of a rostellum and a parenchymatous portion, plus 2 refractile hooklets (arrows). Scale bar represents 10 μm.

Primers CEST3 and CEST5 were used for bidirectional sequencing of the PCR amplification product, as previously described [6]. Amplicons were purified using the Qiagen PCR purification kit (Qiagen, Hilden, Germany) and sequenced using the Microsynth DNA sequencing service (Balgach, Switzerland). Basic Local Alignment Search Tool (BLAST) analysis yielded 98% identity with a sequence from a single reported case in a hominid: a fatal metacestode infection in a captive orangutan (*Versteria* sp., orangutan, Wisconsin; GenBank accession number: KF303341) [7]. Sequence data from the current case were deposited at GenBank (GenBank accession number: MH299497).

Striking similarities in the clinical, radiological, and histopathological features of this case with those of AE, and the high genetic relatedness of *Versteria* and *Echinococcus*, prompted us to manage our patient based on AE literature [8]. Antiparasitic therapy, combined with surgery, are the cornerstones of management. Our patient was treated with albendazole (15 mg/kg/day), to which we added praziquantel (50 mg/kg/day) for combination therapy. After 8 weeks, significant clinical improvement was noted, with complete resolution of both fever and hypotension. A liver magnetic resonance imaging scan performed after 7 months of continuous treatment revealed a 50% decrease in the size of the liver lesion, with residual satellite lesions (Figure 4). Praziquantel is not usually recommended for AE. However, because radical resection of the liver lesion was not possible, we opted for the addition of praziquantel to maximize potential protoscolicidal effects.

Experience with AE suggests that unresected disseminated disease should prompt lifelong antiparasitic treatment. Albendazole sulfoxide drug monitoring proved valuable for optimal dosing and managing toxicity. It was conducted monthly on serum drawn 4 hours post–morning dose (target 1–3 μmol/L) [8].

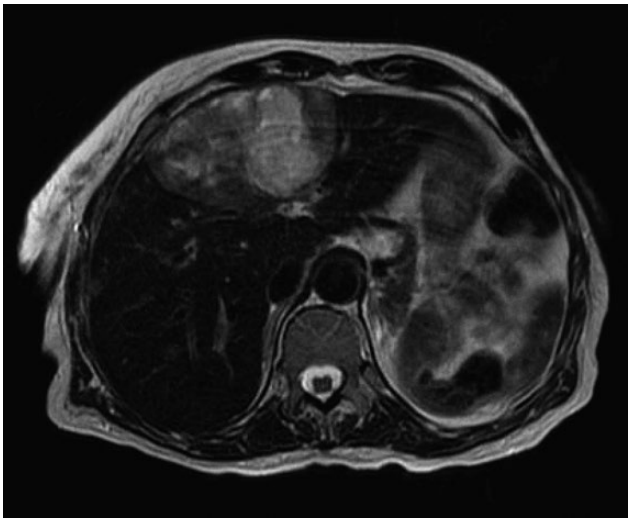

Figure 4. Axial T2-weighted magnetic resonance imaging scan of the liver, showing a large lesion occupying segments 4, with residual satellite lesions 7 months after initiation of albendazole and praziquantel.

Partial liver resection for AE yields poor outcomes [8]. Liver allotransplantation has been performed in the context of complications such as cholangitis, secondary biliary cirrhosis, portal hypertension, hepatic hilar invasion, and Budd-Chiari syndrome, and has shown a 5-year survival rate of 66.7 to 71% [8]. In the current case, these complications were not observed and, after 7 months of combination chemotherapy, we documented a 50% decrease in the size of the liver lesion and resolution of many satellite lesions. Long-term follow-up with imaging and albendazole sulfoxide drug monitoring is planned.

The impact of immunosuppression on infections with metacestodes such as *Echinococcus multilocularis* is well described, often leading to rapidly-invasive progression and dissemination, reminiscent of malignancy [9]. This first human case of *Versteria* sp. infection, particularly in a kidney transplant recipient, is in keeping with these observations, including distant intrathoracic lymph node involvement. A documented normal abdominal CT scan 3 years prior to admission testifies to a relatively rapid disease progression. A *Versteria* infection reported in a captive Bornean orangutan in Milwaukee, Wisconsin, was also rapid, proved fatal, and involved the liver, lung, and spleen, although no immunosuppression was documented [7].

In our case, the patient presented with severe pulmonary and systemic symptoms, presumably attributed to extrahepatic dissemination of the infection. Along with the fever, the patient had multiple episodes of hypotension. We speculate that these episodes may be related to intermittent antigen release, resulting in a type I hypersensitivity reaction as described with *E. granulosus* and, less frequently, with *E. multilocularis*.

The clinical presentation, radiological findings, and inflammatory necrosis seen on histopathology were reminiscent of alveolar echinococcosis, but AE has never been described in humans or animals in the Eastern half of North America [10]. The histopathological appearance of the protoscolex and hooklets were not typical of *E. multilocularis*. Seen in less than 5% of human AE cases, the protoscolex of *E.multilocularis* is a circular, invaginated scolex with rostellar hooks of clearly-defined sizes and shapes (21–20 μm length and a ratio of the basis-length and bow-height of 1:3.4). By contrast, the metacestode of *Versteria* sp. (Figure 3) is a cysticercus-strobilocercus–like larvae whose scolex and rostellar hook dimensions are different from *E. multilocularis* [11]. Positive serology using crude antigens, as well as EgHF antigen for *E. granulosus,* likely reflects cross-reactivity between genera. Cross-reactivity was not observed with the *E. multilocularis* ELISAs, nor in the confirmatory Western blots.

Efforts to better characterize the definitive host of *Versteria* in North America have demonstrated at least 2 circulating parasite genetic lineages, representing separate introductions from Eurasia [12]. The definitive hosts of *Versteria* spp. are wild mustelids (eg, mink, ermine) and the intermediate hosts are rodents.

Sequence analysis of *Versteria* sp. found in feces of an ermine in Colorado, a mink in Oregon, the deceased index orangutan, and our patient all suggest a single lineage [12]. In the United States, *Versteria* sp. has also been reported in Wisconsin and Idaho. While both parasite genetic lineages have been found in the Northwest Territories of Canada, circulation of either has not been described anywhere else in the country [12]. We hypothesize that this immunocompromised patient acted as an accidental host.

Versteria sp. is a newly-recognized zoonosis and must be considered in the differential diagnosis of alveolar echinococcosis in immunocompromised patients from endemic areas. Unlike AE, combination medical therapy without surgery showed promising results. Distinguishing between AE and *Versteria* infection may thus have important prognostic significance.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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