

Pseudoterranova Infestation Beneath Uterine Serosa

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Submitted: 27 March 2021; Accepted: 02 Apr 2021; Published: 08 Apr 2021

Citation: Chihiro Horii, Hideharu Domoto, Hideki Orikasa, Hitoshi Sugiura, Seon-Hye Kim, Yoshimasa Maeno, Hidekazu Takagi and Yutaka Tsutsumi (2021) Pseudoterranova Infestation Beneath Uterine Serosa. *Journal of Clinical Review & Case Reports* 6(4): 612-614.

Abstract

A 49-year-old woman complained of genital bleeding in the follow-up period for her uterine leiomyomas. Close examination disclosed uterine corpus cancer, and biopsy confirmed endometrial carcinoma, grade 1. Total hysterectomy with bilateral salpingo-oophorectomy was performed. Just beneath the uterine serosa, a 9 x 4 mm-sized, yellowish-colored necrotic granuloma containing dead nematode was incidentally observed. Eosinophilic reaction was minimal. The worm was immunoreactive with a monoclonal antibody An-1 against *Anisakis simplex* antigen. Nested polymerase chain reaction using DNA extracted from formalin-fixed, paraffin-embedded sections revealed a gene sequence indicative of *Pseudoterranova decipiens*. *Pseudoterranova*, a larval nematode morphologically similar to *A. simplex*, clinically causes anisakiasis. This is the first case of uterine anisakiasis confirmed morphologically and molecularly.

Keywords: Anisakiasis, *Anisakis simplex*, *Pseudoterranova decipiens*, Uterus

Introduction

The third-stage larval nematode in the genus *Anisakis* is parasitic in a variety of marine creatures, including mackerel, horse mackerel and squid, and the adult form infests the gastric mucosa of marine mammals such as dolphin and whale. Anisakiasis is foodborne disease caused by accidental ingestion of *Anisakis* larvae hidden in raw seafood. The 20 mm-long larval roundworm causes acute abdominal symptoms such as abdominal pain and vomiting. The human is not a suitable host for the *Anisakis* larva and the maturation to the adult never occurs in the human. Therefore, anisakiasis represents a transient infection [1]. Anisakiasis is prevalent in Japan, because of a daily habit eating raw seafood including Sushi and Sashimi [2].

The larvae of the anisakid nematode are categorized in three species: *Anisakis simplex*, *Pseudoterranova*, and *Contracaecum* [1]. *A. simplex* accounts for the majority of human anisakiasis, while the contribution of *Pseudoterranova* and *Contracaecum* is minor [3]. *Pseudoterranova* is minimally invasive with relatively mild clinical symptoms, but the penetration into tissues to cause vomiting and nausea has been reported [2, 3]. Anisakiasis provokes acute gastrointestinal symptoms in most cases, but the anisakid nematode has been reported to be found asymptotically in the abdominal cavity [4]. It may form a mass in the abdominal cavity causing intestinal obstruction [5].

To the best of our knowledge, no report has described anisakiasis in the uterus. We present herein a case of incidental uterine anisakiasis. The dead larva was seen just beneath the serosal surface of the resected uterus harboring leiomyomas, adenomyosis and endometrial cancer. Immunohistochemical and molecular analyses confirmed the infestation of *Pseudoterranova decipiens*.

Case Presentation

A 49-year-old Japanese woman complained of genital bleeding. She had a history of uterine leiomyomas and was followed up at the outpatient clinic of obstetrics and gynecology of Kawasaki Municipal Hospital, Kawasaki, Japan. Endometrial biopsy confirmed endometrial carcinoma, grade 1 (clinical stage IA). She denied keeping dogs or other animal pets.

Total hysterectomy with bilateral salpingo-oophorectomy was soon performed. Multiple leiomyomas up to 38 mm in size were found in the myometrium. An exophytic polypoid lesion in the uterine body microscopically consisting of irregularly fused atypical glands was diagnosed as endometrioid carcinoma, grade 1. It showed involvement of the adenomyosis; however, true myometrial invasion was only limited to the shallow part of the myometrium (histological stage 1A). Incidentally, a 9 x 4 mm-sized yellowish-nodule was found immediately beneath the serosa of the uterus (Figure 1a, yellow arrow). Histologically, an encapsulated necrotic mass was surrounded by abortive epithelioid granuloma, and contained a dead 0.5 mm-wide nematode worm (Figure 1b). Details of microscopic morphology were indistinct due to total necrosis, but the presence of a thick outer muscle layer was recognized. Mild lymphoplasmacytic reaction was seen outside the epithelioid cell layer, but with minimal eosinophilic infiltration. Charcot-Leiden's crystals were absent. Elastica van Gieson stain failed to demonstrate a vascular elastic lamina in or around the lesion.

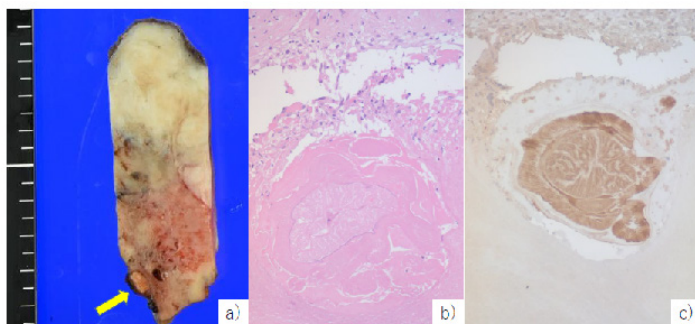


Figure 1: Uterine lesions. Gross findings (cut surface) of the uterus (a). A yellowish-nodule is seen just beneath uterine serosa (yellow arrow). The microscopic features of subserosal parasitic granuloma (b: H&E, c: immunostaining using a monoclonal antibody An-1). A dead 0.5 mm-wide nematode is found within the nodule surrounded by abortive epithelioid cell granuloma (b). Eosinophilic reaction is scarcely observed. The worm is clearly labeled with the monoclonal antibody (c).

At first, infestation of *Dirofilaria immitis* (dog heartworm) was suspected microscopically. DNA was extracted from formalin-fixed, paraffin-embedded sections of the necrotic nodule, and polymerase chain reaction (PCR) using the nested primer pairs specific for

the internal transcribed spacer-1 (ITS-1) region between the 18S and 5.8S ribosomal RNA genes was evaluated. However, no PCR product was obtained. Next, immunohistochemical staining using an amino acid polymer technique (Simple Stain-Max; Nichirei, Tokyo) was applied. A monoclonal antibody An-1 against *A. simplex* diluted at 1: 1,000 was incubated overnight after heat-assisted antigen retrieval in 1 mM ethylenediamine tetraacetic acid solution, pH 8 [6, 7]. The worm showed clear positivity (Figure 1c). Subsequently, nested PCR using two sets of the primer pairs for the ITS-1 region was applied to target the *A. simplex* gene. In the first round, forward and reverse primers were 5'-AAGTCTC-CCAACGTGCATACCATC-3' and 5'-ATGGCACGTCTGGCT-GAGGGTCTGA-3', respectively. In the second round, those were 5'-GTTGAACAACGGTGACCATTGTTGGC-3' and 5'-GTA-CAAATCTTGGCGGTGGATCACTC-3', respectively. A 225 bp PCR product (Figure 2a) was successfully obtained. The sequence of the PCR product showed 100% match with DNA of *Pseudoterranova* spp. by NCBI BLAST search analysis. In addition, the phylogenetic tree analysis of *A. simplex* partial ITS-1 region, 5.8S rRNA gene was conducted by MEGA X software based upon maximum likelihood method and Tamura-Nei model as described elsewhere (Figure 2b) [8]. The DNA sequence of the present case belongs to the clusters of *Pseudoterranova decipiens*.

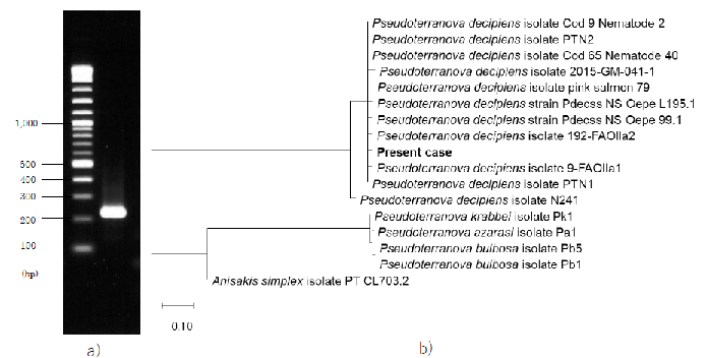


Figure 2: Final PCR product by nested PCR (a). The phylogenetic tree analysis of *A. simplex* partial ITS-1 region, 5.8S rRNA gene conducted by MEGA X software (b).

Discussion

This is the first report describing *Pseudoterranova* infestation beneath the uterine serosal surface. The rare species of the anisakid nematodes was confirmed by morphological and molecular studies. Extraintestinal anisakiasis is infrequently experienced [1]. *Pseudoterranova*-induced extraintestinal anisakiasis seems to be extremely rare. Most of the extraintestinal lesions have been caused by *A. simplex*, since *A. simplex* is more invasive than *Pseudoterranova* and *Contracaecum* and is prone to manifest mild symptoms such as abdominal pain and vomiting [1-3]. To best of our knowledge, extraintestinal *Pseudoterranova* migration has been reported in the aortic wall, soft tissue of inguinal region and in the liver [9-11].

Extraintestinal anisakiasis is a disease in which an anisakid nematode larva penetrates the intestinal wall and migrates into the abdominal cavity to reach intraperitoneal organs such as the liver, omentum, and ovaries. In the liver, the larvae were found

in the portal vein, so that the pathway via the portal vein has been proposed [12]. In the present case, the *Pseudoterranova* larva finally moved to the uterine serosa. The rarity of uterine infestation by *Pseudoterranova* may be related to the physical distance between the upper digestive tract and the uterus and also to the physical tightness of the uterine serosa.

Anisakiasis may accompany allergic symptoms such as urticaria and nausea without abdominal pain [1]. In such cases, the clinical diagnosis of anisakiasis is supposed to be difficult. In the present case, eosinophilic tissue reaction was minimal, and neither abdominal nor allergic symptoms were noted. Anisakiasis was thus not suspected before surgery. There might be a considerable number of asymptomatic anisakiasis as was so in our case [1-3].

Considering the current situation where the Japanese food culture eating raw seafood is spreading worldwide, the extraintestinal *Pseudoterranova* parasitism might be increasing in areas outside Japan.

Conflict of Interest Statement

The authors do not have any conflicts of interest to declare in relation to the present report. There were no sources of funding for reporting of the present case.

Statement of Ethics

The patient provided a written informed consent for the publication of this case report. The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Author Contributions

We declare that all the authors made a substantial contribution to the concept of the case report or interpretation of data and approved the version to be submitted. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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