

CASE REPORT

A Fishy Tale of Macrocytosis

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Abstract

Diphyllobothriasis is a rare fish tapeworm infection, yet one of the most important fish-borne human diseases due to the high morbidity and commonly missed diagnosis. It occurs by ingesting infected uncooked fish. Several fish tapeworm species can affect humans, with the most prevalent of these being *Diphyllobothrium latum* found in pike, perch, and arctic char. In humans, the worm attaches to the small bowel where it can live undetected for 10 to 15 years and can grow as long as 15 meters. While in the small bowel, it competes with the host for vitamin B12, leading to vitamin B12 deficiency and macrocytosis. The signs and symptoms of infestation are often vague and non-specific, making for a challenging diagnosis. Furthermore, physical examination and laboratory investigations are typically unremarkable. We describe only the fourth case report of *D. latum* in Canada. It occurred in an otherwise healthy patient with a two-year history of vague abdominal pain, diarrhea, low B12, and macrocytosis. The patient was an avid sushi eater and remained symptomatic and undiagnosed during this time. Spontaneous passage of the worm and treatment with praziquantel ultimately led to resolution of her symptoms.

Case Presentation

A 43-year-old woman presented to her family physician with a two-year history of fatigue, diarrhea, and constant dull abdominal discomfort. Stools were described as normal in frequency and intermittently loose in consistency. In addition, she also experienced two to three episodes per month of non-bloody painless diarrhea, which was associated with a cramping abdominal pain. She attributed this pain, which radiated to the back and pelvis, to her menstrual cycle. During this period, she did not have any nausea or vomiting and did not notice any change in weight or appetite.

The patient, a marine biologist with an extensive travel history, noticed that her symptoms began after a busy year of fieldwork in Iceland, Denmark, and the Arctic, during which she began regularly consuming raw sushi and sashimi. She was a nonsmoker and only occasionally consumed alcohol. She was otherwise in good health and did not take any medications or over-the-counter supplements. Her past medical history was significant for a prior myomectomy eight years ago for fibroids. Clinical examination was unremarkable and revealed no neurologic findings or evidence of bruising, bleeding, or stigmata of chronic liver disease.

Initial laboratory investigations yielded the following results: Hgb 133 g/L, RBC $3.6 \times 10^9 \text{ L}^{-1}$, MCV 101.0 fL, MCH 35 pg, WBC $4.7 \times 10^9 \text{ L}^{-1}$, and platelets $178 \times 10^9 \text{ L}^{-1}$. Serum creatinine, electrolytes, lipase, thyroid and liver function tests were within normal limits. Serum vitamin B12 was 157 pmol/L (N: 156-672 pmol/L), compared to a level of 435 pmol/L two years

previously. Anti-tissue transglutaminase antibody (IgA normal) was negative, as were tests for Lyme disease and infectious mononucleosis. Due to her significant change in B12 level, she was treated with supplemental vitamin B12 for suspected pernicious anemia. Vitamin B12 levels returned to baseline although she remained macrocytic.

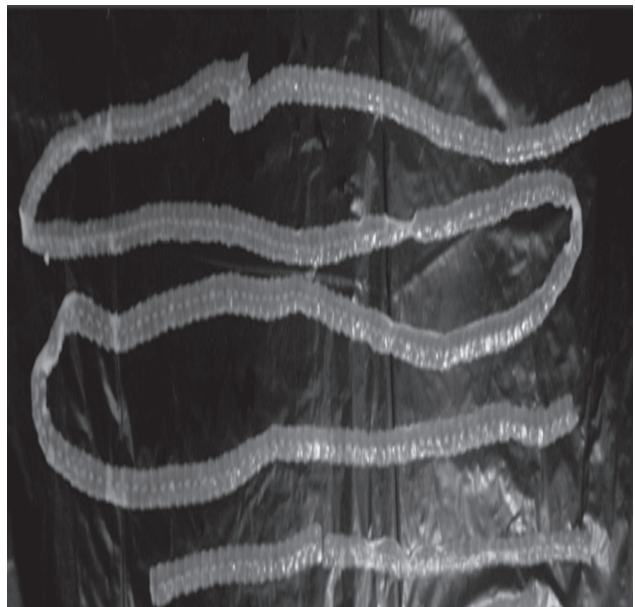


Figure 1. *D. latum* specimen measuring 1.6 meters collected from patient's stool sample.

Several months later she again experienced painless diarrhea. This time, however, she spontaneously passed a 1.6 meter long tapeworm later identified as

Diphyllobothrium latum (Figure 1). She was treated with a single dose of praziquantel (10 to 25 mg/kg and follow-up stool tests for ova and parasites done two weeks later were negative. Investigations several months after she passed the worm revealed that her vitamin B12 deficiency, macrocytosis, and presenting symptoms had resolved.

Literature Search

All available literature concerning diphylobothriasis cases in Canada was assessed using the MEDLINE database through the PubMed interface. The literature search was conducted using the terms “diphyllobothriasis OR fish tapeworm AND Canada” and was restricted to the English language and to human subjects. A total of 12 studies were obtained, only three of which contained human case reports of fish tapeworm infestation in Canadians. References of these studies were also reviewed for relevant literature. Results of the search are summarized in Table 3.

Discussion

Macrocytosis

Macrocytosis is defined as the average size of red blood cells (RBCs) being greater than normal (MCV>100fL). It is most commonly seen in the setting of folate deficiency in alcohol abuse, liver disease, and during chemotherapy. However, macrocytosis can have many causes and is categorized histologically into either normoblastic or megaloblastic according to the morphology seen in the bone marrow (Table 1). Cells of normoblastic conformation are characterized by a normal nuclear to cytoplasm ratio indicating unimpaired DNA synthesis. In megaloblastic cells, on the other hand, DNA synthesis is impaired resulting in cells with delayed nuclear maturation and decreased nuclear to cytoplasm ratios.¹

Normoblastic	Megaloblastic
Alcohol abuse	Vitamin B12 deficiency
Liver disease	Folate deficiency:
Hypothyroidism	- poor nutrition (alcoholism)
Multiple myeloma	Drugs:
Myelodysplastic syndrome	- Dihydrofolate reductase inhibitors
Reticulocytosis	- Anticonvulsants
	- Oral contraceptives
	- Certain HIV medications

Table 1. Causes of macrocytosis

Vitamin B12 deficiency

Folate and vitamin B12 deficiency play a pivotal role in DNA regulation and are the two most common causes of megaloblastosis.²⁻⁴ Vitamin B12 is obtained from animal dietary sources and has a complicated mechanism of absorption. The acidic milieu of the stomach first facilitates release of dietary B12 from food. Vitamin B12 then binds to an intrinsic factor produced by gastric parietal cells, allowing it to ultimately be absorbed in the terminal ileum. A variety of different factors can interfere with these steps and lead to vitamin B12 deficiency (Table 2).⁵

- Dietary (veganism)
- Autoimmune (pernicious anemia)
- Total/partial gastrectomy
- Ileal resection
- Pancreatic insufficiency
- Celiac disease
- Crohn’s disease
- Blind loop syndrome
- Tropical sprue
- Fish tapeworm (*D. latum*)

Table 2. Causes of vitamin B12 deficiency

Diphyllobothriasis

Diphyllobothriasis is a clinical syndrome associated with the *Diphyllobothrium* parasite, and is acquired by ingestion of contaminated raw or uncooked fish. Eggs of *D. latum* have been found in humans as early as 4000 BC and more than 20 million people are estimated to carry the fish tapeworm.^{6,7} Once prevalent many years ago, diphylobothriasis rates have since drastically decreased due to modern cooking and fish transport regulations. However, endemic regions still persist in some communities in Northern Europe, Asia, and the Arctic. Furthermore, the increasing popularity of raw fish cuisine like sushi has set the stage for a potential worldwide resurgence of *D. latum*.⁸ To the best of our knowledge, this is only the fourth case report describing *D. latum* infestation in Canada and only the second resulting from sushi consumption (Table 3).⁹⁻¹¹

Although there are several species that can affect humans, the most prevalent of these is *Diphyllobothrium latum* found primarily in pike, perch, turbot and arctic char. The life cycle of *D. latum* involves multiple larval stages and hosts. Worm ova first hatch into embryos in freshwater.¹⁰ They are then ingested by small crustaceans, or copepods, where they mature

to the first larval stage. When copepods are ingested by larger fish, the larvae invade fish muscle fibers and mature into the second larval stage called plerocercoids. Consumption by humans of raw fish infected with plerocercoids allows the larva to attach to the walls of the host's small intestine and mature to adult tapeworms within three to five weeks. When mature, *D. latum* can grow anywhere from two to 15 meters in length making them the longest known human parasites. In humans, the adult parasites continue to grow, release ova, and may live undetected for 10 to 15 years.^{11,14}

Symptoms and Investigations

Diagnosis of diphyllbothriasis is often difficult due to the asymptomatic nature and the subtle findings of the disease. Only 20% of patients experience any symptoms, which are often mild, non-specific, and can include fatigue, diarrhea, constipation, vague abdominal pain, and headaches. Physical examination and laboratory investigations are typically unremarkable and can further complicate making the diagnosis.

Longstanding infections with *D. latum* may lead to macrocytic anemia, although the mechanism is not yet fully understood. The anemia is believed to be due

to the dissociation of the vitamin B12-intrinsic factor complex in the gut lumen facilitated by the parasite. The worm then preferentially absorbs B12 in a 100:1, ratio making it unavailable to the host. Despite this, low B12 levels are only seen in about 40% of individuals infected with *D. latum*, and only 2% of patients will be clinically anemic.¹⁵ The distressing spontaneous passage of the tapeworm, as was the case in our patient, is often the only clinical sign of infection.^{16,17} Occasionally, patients may also see segmental chains in their stools. The gold standard for diagnosing *D. latum* involves using molecular methods to identify ova or worm segments in the stool.¹¹

Treatment

Treatment of *D. latum* involves a single dose of 10-25 mg/kg of praziquantel. Stool specimens are then monitored at one and two weeks for ova, and should be negative after treatment. Otherwise, a second dose of praziquantel is indicated.

Prevention

Avoiding raw, uncooked or smoked fish is the most effective way to prevent diphyllbothriasis. If uncooked, the Fish and Fishery Products Hazards and Controls Guide recommends that fish be either frozen to a temperature less than -20°C for seven days or to

Reference	Year	Description	Presentation	Time to diagnosis	Risk factors	Treatment	Resolution
Cushing and Bacal ¹²	1934	Retrospective observational study, 50 cases	39 passed worm segments in stool, 27 complaints of vague abdominal symptoms	Unknown	Jewish women and Findlanders, tasting raw fish to ensure proper seasoning before cooking	Male fern, kamala, pelletierin tannate, and santonin	Passage of worm with intact scolex
Turgeon ¹³	1974	Retrospective observational study, 9 cases	Asymptomatic, passage of worm segments, vague abdominal discomfort	Unknown	Raw salted fish consumption	Niclosamide	Passage of worm with intact scolex
Craig ⁹	2012	Single case report	Spontaneous passage of worm, asymptomatic, fatigue, constipation, vague abdominal discomfort	8 weeks	Raw sushi and sashimi consumption	Praziquantel (25 mg/kg)	Stool test 2 weeks after passage of worm revealed no ova

Table 3. Reported cases of *D. latum* infection in Canada.

a temperature of less than -35°C for 15 hours prior to consumption.¹⁸

Conclusion

Diphyllobothriasis is a fish tapeworm infection that occurs after ingesting infected raw or uncooked fish. In human hosts, the worm competes for vitamin B12 and can lead to vitamin B12 deficiency and macrocytosis. Signs and symptoms are often non-specific, and infection can persist undiagnosed for many years. Although a rare cause of vitamin B12 deficiency, diphyllobothriasis should be considered in the differential for unexplained cases of macrocytosis, as it is a treatable cause of vitamin B12 deficiency.

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