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Through the Looking Glass: A Child With Arthralgia, Malaise and Weight Loss

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CASE

A 17-year-old immunocompetent female presented with symptoms of extreme fatigue, headache, dizziness, weight loss of 6 kg, and arthralgia in her wrist and knee joints. She had no fever or abdominal complaints. These symptoms started after 2 weeks of abdominal pain, diarrhea, and nausea, which were self-limited. Her medical history was noncontributory. Family history showed that her mother was diagnosed with Crohn's disease in the past but was currently asymptomatic without the use of medications. There was no travel history.

At presentation, her vital signs were normal. Her body mass index was 16.7. Physical examination revealed no abnormalities.

Laboratory tests showed a hemoglobin of 6.9 mmol/L (7.5–10.0), leukocytes of 14.9×10^9/L (4.0–10.0) with a differential of 91% neutrophils, 3% monocytes, 1% eosinophils and 5% lymphocytes, thrombocytes of 588×10^9/L (150–400), iron of 4 umol/L (9–30) and erythrocyte sedimentation rate (ESR) of 22 mm/h (0–20). C-reactive protein (CRP) was elevated to 74 mg/L. Other laboratory tests including mean corpuscular volume, reticulocytes, ferritin, transferrin, transferrin saturation, folic acid, thyroid function, liver transaminases, kidney function, albumin and immunoglobulin A, G and M were all normal. Feces calprotectin was 66 mg/kg (0–50). Serologic testing for cytomegalovirus and Epstein-Barr virus was negative. The helicobacter pylori antigen test was negative in feces.

One month later the patient was seen at the outpatient clinic with ongoing complaints. Laboratory tests were repeated showing a hemoglobin level of 7.4 mmol/L (7.5–10.0), ESR of 8 mm/h (0–20) and a persistently elevated CRP of 68 mg/L. An abdominal ultrasound was normal, and an abdominal MRI showed some slightly enlarged mesenterial lymph nodes with normal terminal ileum. Given the family's history of maternal Crohn's disease, an esophagogastroduodenoscopy and colonoscopy were performed to exclude an inflammatory bowel disease. A macroscopic examination of the duodenum showed irregular mucosa with focal active inflammation, the rest of the gastrointestinal tract appears to be normal. Microscopic examination of the duodenal biopsies revealed blunted villi with distention of the lamina propria and dilated lacteals (Fig. 1A). Some of the colon biopsies showed a mild chronic inflammation with scattered microgranulomas. Other biopsies were normal. The pathologist performed additional diagnostic tests that confirmed the diagnosis.

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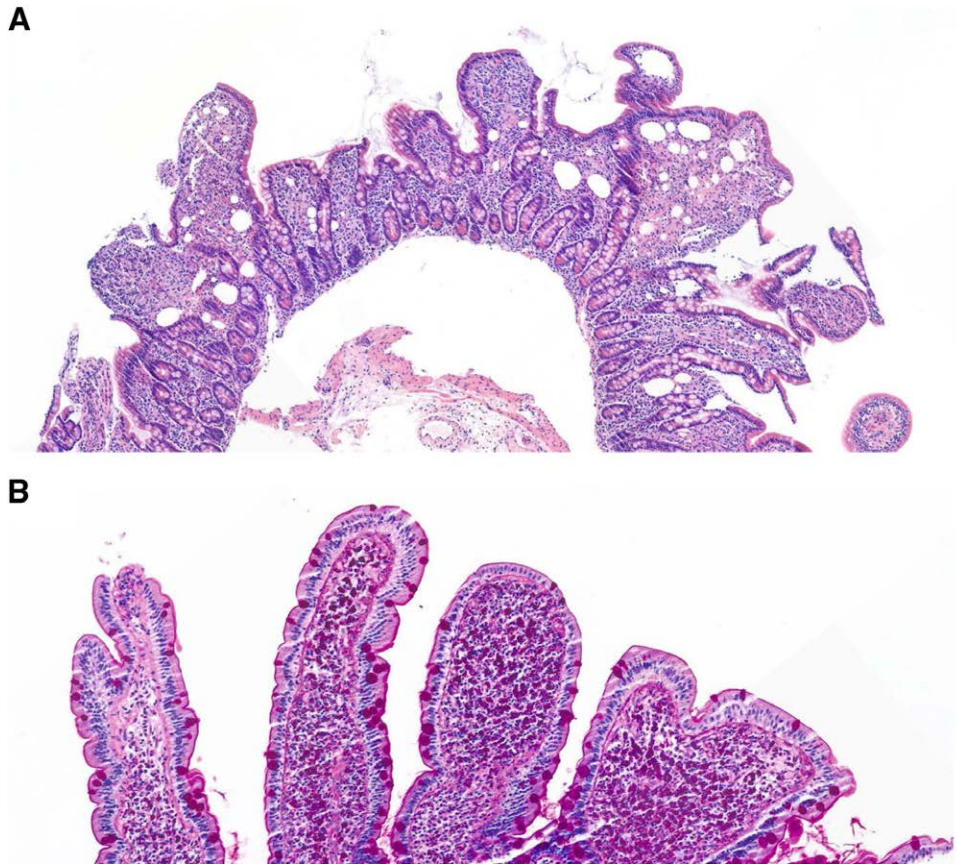

FIGURE 1. A: Duodenal biopsies [hematoxylin & eosin stain (HE stain), 10××x] with blunted villi with distention of the lamina propria and dilated lacteals. B: PAS staining (20×) highlights the presence of foamy macrophages, filled with bacterial inclusions.
PAS, periodic acid-Schiff. full color online

DENOUEMENT

In biopsy specimens from the duodenum, cecum, colon, and sigmoid, periodic acid-Schiff (PAS) staining highlighted the presence of foamy macrophages, filled with bacterial inclusions (Fig. 1B). Staining with CD68 showed an increased presence of macrophages. Grocott's silver stain and Ziehl-Neelsen stain were both negative.

PAS-positive foamy macrophages in duodenal biopsies can be seen in a number of conditions, including leishmaniasis, endemic mycoses (e.g. *Histoplasma capsulatum*), mycobacterial infections (e.g. *Mycobacterium avium)*, malakoplakia, as well as various storage diseases. However, given a lack of relevant travel history, a negative medical history and no suspicion of immunocompromised status, these infections and causes were presumed to be less likely. PAS-positive foamy macrophages in duodenal biopsies are also characteristic of intestinal Whipple's disease. In our patient the polymerase chain reaction (PCR) for *Tropheryma whipplei (T. whipplei)* of the duodenal biopsy tissue was positive, and in combination with the chronic symptoms, this established the diagnosis of classic Whipple's disease (WD). Hematoxylin and eosin (HE) stain was negative for co-infection with *Giardia lamblia*, and the presence of endocarditis was excluded with a transthoracic ultrasound. Liquor showed a negative PCR for *T. whipplei*, making central nervous system (CNS) involvement less likely. Treatment was started with ceftriaxone 100 mg/kg/day intravenously for 14 days, followed by oral treatment with trimethoprim-sulfamethoxazole for one year. The duodenoscopy at the end of the treatment showed no macroscopic and microscopic abnormalities and the PCR was negative for *T. whipplei.*

WD, an infection caused by the bacterium *T. whipplei*, is mostly described in adults. The bacterium belongs to the group of Actinobacteria and is an environmental microorganism found in soil, freshwater or seawater sediments.[1] Transmission probably occurs from human-to-human mainly by the fecal-oral and oral-oral routes. There are 4 commonly recognized manifestations of WD, namely acute transient infection, asymptomatic carriage, localized extra-intestinal infection and the classic form.[2]

Acute transient infections, including gastroenteritis and bacteremia, affect more children than adults.[2] This is the most described entity of WD in pediatrics, mainly in studies from France and some countries in Africa.[1,3,4] Two studies performed in France showed that *T. whipplei* was associated with acute diarrhea in young children by finding a positive PCR for *T. whipplei* in feces. Without treatment, the children recovered rapidly.[3,4] Only one of the studies analyzed postdiarrheal stool specimens showing a negative PCR for *T. whipplei* after a month.[3] In a study from Senegal, *T. whipplei* DNA was reported in 6.4% of blood samples of 204 patients, mainly children, with unexplained fever.[5] Similar studies in Senegal and Gabon reported *T. whipplei* DNA-positive blood samples in respectively 4.6% (36 of 786 patients) and 0.2% (1 of 410 children) of, mainly pediatric, febrile patients.[6,7] The diagnosis of an acute infection is established on clinical symptoms in combination with a positive PCR for *T. whipplei* from fecal samples (in case of gastroenteritis) and blood (in case of bacteremia). The culture of *T. whipplei* is difficult and not readily available in a routine microbiology laboratory. The existence of other forms of acute *T. whipplei* infections and the possible long-term sequelae of acute infections are currently unknown due to a lack of data.

Asymptomatic carriage rate of *T. whipplei* occurs with a variable prevalence in the gastrointestinal and respiratory tract in adults, but the true prevalence in children is not known. One study performed in France detected a carriage rate of 1.7% in rectal swabs of 3241 children without diarrhea.[4] The prevalence of positive stool samples of asymptomatic young children in Senegal, Laos and Ghana were higher, respectively 75%, 48% and 27.5%.[8–10] The carriage rate decreases in older age groups.[1,2] Although a good explanation is not yet found for these differences in prevalence, poor sanitation and sandbox contacts are mentioned as possible factors. Of note, the bacterial load in fecal samples is lower in asymptomatic carriers than in symptomatic patients with *T. whipplei* infections.[2]

A localized extra-intestinal infection is defined as a positive PCR for *T. whipplei* in a specimen from an extra-intestinal organ without systemic involvement and/or the specific histological lesions in the small-bowel biopsies specimens as seen in classic WD.[11] In adults it can occur in almost every organ, but data in pediatrics are scarce. Two case reports have described localized *T. whipplei* of the CNS infection in immunocompetent boys 4 and 6 years of age, who fully recovered after antibiotic treatment.[12,13] Another report has described a child with HIV and a high plasma viral RNA load who died of a localized *T. whipplei* infection of the CNS.[14]

The classic form of WD is a rare, chronic infection of the intestinal tract that typically affects middle-age Caucasian men. The estimated prevalence is 3 per 1 million (95% 2.1–3.8).[1]

The most common features are chronic gastrointestinal complaints such as diarrhea and abdominal pain, joint symptoms and weight loss.[1] Typical course of classic WD starts with arthritis and/ or arthralgia many months or even years before the onset of gastrointestinal manifestations, but often it does not present typically. Patients are often misdiagnosed as having rheumatic disease and treated with immunomodulatory drugs.[2] A delay in the diagnosis of classic WD could lead to disseminated forms of the disease with CNS manifestations and other severe complications, often limiting recovery and prognosis.

A genetic predisposition plays probably a role in the susceptibility to infection, given the fact that the incidence of classic WD is not higher in asymptomatic carriers in comparison with healthy individuals.[1] Classic WD is definite if the PAS and/or specific immunohistochemistry and PCR *T. whipplei* are positive in small-bowel biopsies in combination with symptoms suspect for WD.

In pediatrics, the classic form is extremely rare. One case report described a 4-year-old immunocompetent girl, who developed chronic diarrhea and hematochezia. The coloscopy showed chronic colitis. Due to a family history of Crohn's disease, this was interpreted as ulcerative colitis and immunomodulatory treatment was started. Subsequently, her condition deteriorated and an esophagogastroduodenoscopy was performed showing foamy macrophages in the duodenal biopsies. The specimen was PAS positive, Ziehl-Neelsen staining negative, and PCR positive for *T. whipplei*, confirming the diagnosis of classic WD. Her symptoms disappeared after antibiotic treatment.[15] To the best of our knowledge, our patient is the second pediatric patient described in the literature with the diagnosis of classic WD with chronic symptoms of arthralgia, weight loss and a period of abdominal complaints in combination with the PAS-positive and *T. whipplei* PCR-positive small-bowel biopsies.

Treatment recommendations for localized and classic WD are based on limited evidence, but both forms use a regimen of ceftriaxone or meropenem for 14 days, followed by oral trimethoprim-sulfamethoxazole for 12 months or a combination of doxycycline and hydroxychloroquine for 1 year in case of resistance to trimethoprim-sulfamethoxazole.[1] Although relapses were described in the past, the prognosis after antibiotic treatment is in general good with clinical remission. Untreated WD is supposed to have a fatal course.[1]

In conclusion, WD is believed to be extremely rare in pediatrics, but the true incidence is not known and could be underestimated because children are not routinely tested for this pathogen.

WD must be considered in case of chronic symptoms of weight loss and intestinal symptoms, in cases of suspected autoimmune diseases deteriorating after the use of immunosuppressive therapy and in the case of an unexplained single organ infection.

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