Iatrogenic *Trichuris suis* Infection in a Patient With Crohn Disease

Richard L. Kradin, MD; Kamran Badizadegan, MD; Pavan Auluck, MD; Joshua Korzenik, MD; Gregory Y. Lauwers, MD

• We report a case of biopsy-proven iatrogenic infection by the pig whipworm *Trichuris suis* in a patient with Crohn disease. The deliberate therapeutic ingestion of *T suis* ova has been adopted as an experimental approach to the treatment of Crohn disease in an effort to promote a switch from the T helper subtype 1 to T helper subtype 2 inflammatory phenotype in vivo. This report examines the morphology of the immature and adult *T suis*, the effects of this intervention on the immunophenotype of the bowel mucosa, and it also raises the possibility of persistent active infection in man.

(*Arch Pathol Lab Med.* 2006;130:718–720)

REPORT OF A CASE

A 16-year-old adolescent boy was admitted to the Massachusetts General Hospital for evaluation of Crohn disease. He had been well until age 9, when he developed rectal pain with bleeding and an anal fissure. A diagnosis of Crohn disease was established by sigmoidoscopy and biopsy. He was treated with 5-acetylsalicylic acid, which controlled his symptoms for several years. When his disease flared, a regimen of cyclosporine was begun, but the patient had little improvement. Subsequently, he received infliximab (Remicade) and intravenous corticosteroids, but developed anaphylaxis with repeated doses. His disease was successfully managed for a year with corticosteroids and methotrexate. When it flared again, he sequentially received thalidomide, azathioprine, and adalimumab (Humira), all with limited success.

Six months prior to admission, he presented to this hospital with chronic diarrhea and abdominal pain. Physical examination was remarkable for abdominal tenderness on palpation. At that time, he and his family expressed eagerness to consider treatment with *Trichuris* ova. He received 5 oral doses of 2500 *T suis* ova off protocol.

Subsequently, he was admitted to the hospital for further workup and colonic biopsy. Physical examination revealed modest tenderness on abdominal palpation, but was otherwise unremarkable. Hemoglobin was 11.1 g/dL with hematocrit of 35%. The white blood cell count was 8.1 mm^3 with 70% polymorphonuclear leukocytes, 17% lymphocytes, 10% monocytes, and 3% eosinophils. The absolute eosinophil count was 210/μL. The erythrocyte sedimentation rate was 61 mm/h. A computerized tomographic scan of the abdomen showed thickening of the walls of the terminal ileum, descending colon, and rectum.

A colonoscopy revealed diffuse colonic disease ranging in severity from mild to high. A broad linear rectal ulcer was noted; there was a tight stricture at 25 cm. Biopsies were taken at the level of the ileocecal valve and of the ascending and descending colon.

MATERIALS AND METHODS

Ileal and colonic biopsy tissue of the ileocecal region and left and right colon was fixed in 10% buffered formalin, dehydrated, and embedded in paraffin. Sections were stained with hematoxylin-eosin. Immunohistochemical studies were performed on deparaffinized sections using an avidin-biotin-peroxidase complex technique. Primary monoclonal antibodies included anti-CD4, anti-CD8, and anti-CD20 (Becton Dickinson, Franklin Lakes, NJ).

PATHOLOGIC FINDINGS

Pathologic evaluation showed that several round helminthic forms were identified directly beneath attenuated ileocecal mucosal epithelium, with no evidence of intraluminal growth of the nematode (Figure 1). The crypts adjacent to the nematode showed mild dilatation and mucus inspissation.

High-power examination of the ileal biopsy tissue revealed a thin, striated, 3- to 5-μM cuticle. The cuticle was focally thickened to form a bacillary band (Figure 1, small arrow). A capillary esophageal lumen was identified within the cytoplasm of a stichocyte (Figure 1, large arrow). The size of the helminth, its superficial attachment to the bowel mucosa, and the presence of stichosomal elements were consistent with infection by an immature trichurid.

The cecal biopsy showed fragments of a coiled sexually mature adult trichurid. Fragments of the thin anterior segment of the helminth showed a well-developed stichosome (Figure 2, A, black arrow) with striated cuticle and bacillary band (Figure 2, A, white arrow) and a muscular triradiate esophagus (not shown). A section of the posterior segment of the nematode showed the annular cuticle (Figure 2, B, black arrow), holomyarian muscle, testis (Figure 2, B, arrowhead), and intestine (Figure 2, B, white arrow) of an adult male trichurid. There was no evidence of helminthic infection of the left colon.

All of the biopsies showed mild-to-moderate chronic inflammation with architectural distortion of mucosal glands (Figure 3, A). Focal ill-defined histiocytic aggregates (Figure 3, A, arrow) were identified in the cecum. Increased mucosal eosinophils were identified at all sites (Figure 3, B). Immunohistochemical findings showed a marked predominance of $CD4^+$ lymphocytes in the infil-

Accepted for publication January 9, 2006.

From the Departments of Pathology (Drs Kradin, Badizadegan, Auluck, and Lauwers) and Medicine (Drs Kradin and Korzenik), Massachusetts General Hospital, Boston.

The authors have no relevant financial interest in the products or companies described in this article.

Reprints: Richard Kradin, MD, 55 Fruit St, Warren 253, Massachusetts General Hospital, Boston, MA 02114 (e-mail: rkradin@partners.org).

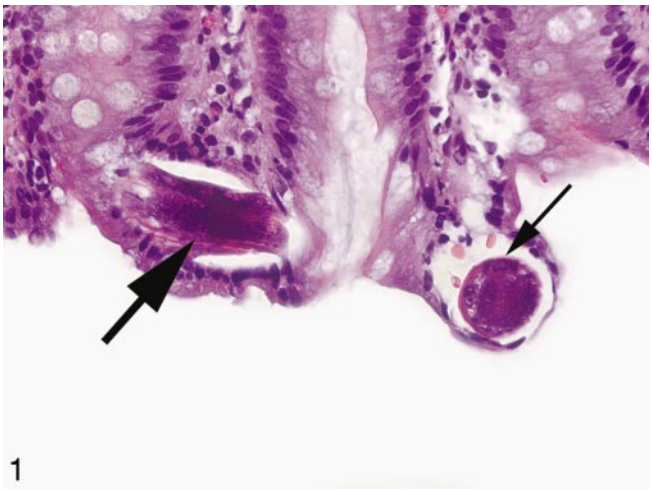

Figure 1. *Two nematodes are located beneath the attenuated ileocecal mucosal epithelium. The cuticle is focally thickened to form a bacillary band (small arrow). The stichosome and esophagus is evident (large arrow) (hematoxylin-eosin, original magnification ×500).*

trates with small numbers of $CD8^+$ and $CD20^+$ lymphocytes (not shown).

COMMENT

The morphologic features of the nematode helminth in this case were consistent with iatrogenic infection by *T suis*. Morphologically, *T suis* closely resembles *Trichuris trichiura*, the species that parasitizes man. Following ingestion of embryonated trichurid ova, larvae hatch in the small bowel and subsequently migrate into the cecum, where they become sexually mature. However, trichuriasis may occur in the terminal ileum and in the length of the colon.

Adult trichurids are pink-gray and range in size from 3.0 to 5.0 cm. The female is slightly larger than the male.[1] The lay term *whipworm* derives from the fact that the anterior segment of the adult *Trichuris* is long and attenuated, resembling the end of a whip, whereas the posterior segment of the worm is short and thick, resembling its handle.

Morphologically, a short triradiate, muscular esophagus develops a capillary tubular lumen that extends within the specialized glandular epithelium of a stichosome that is evident by light microscopy. The subcuticular region of

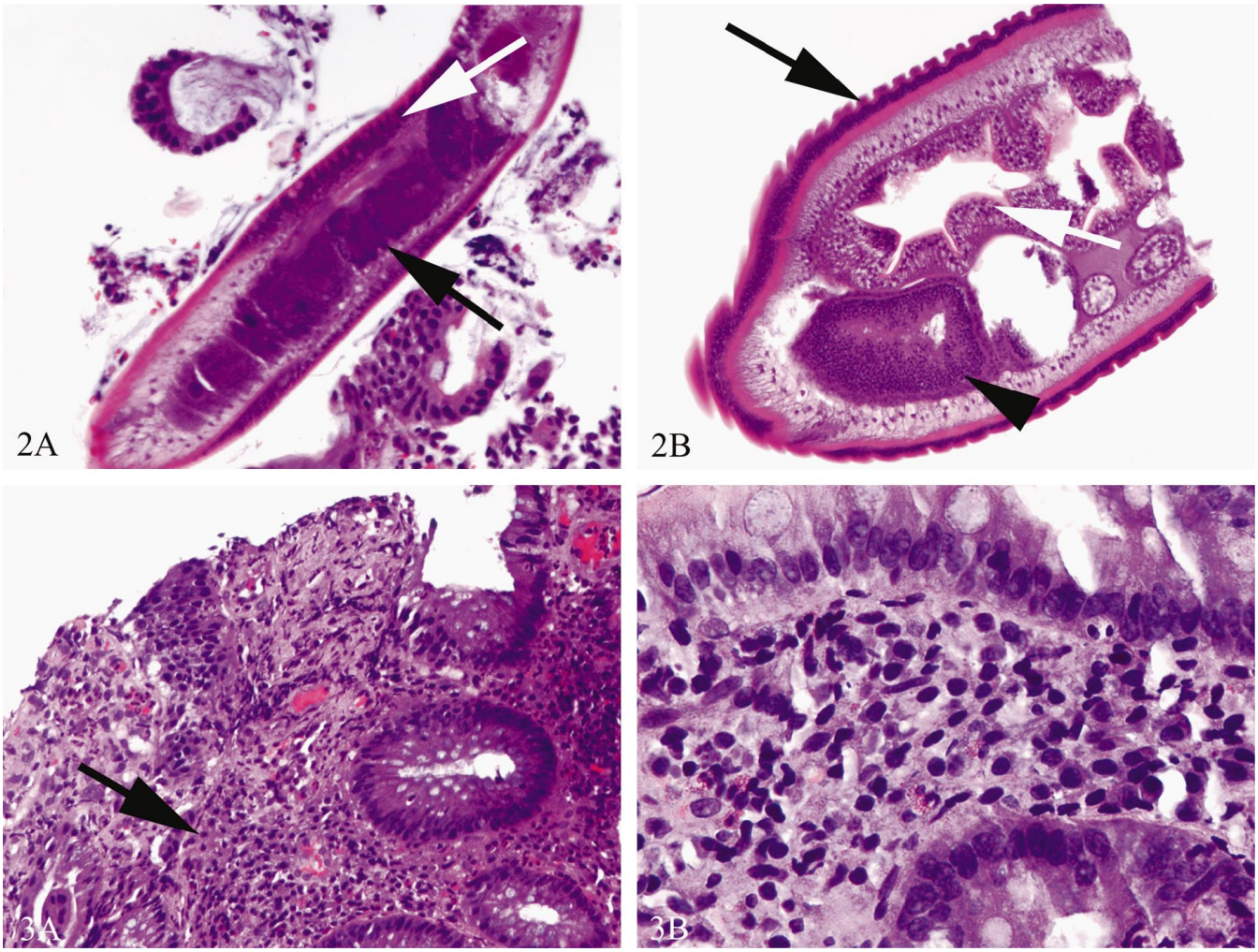

Figure 2. *A, The anterior segment of an adult male* Trichuris *shows a well-developed stichosome (black arrow), striated cuticle, and bacillary band (white arrow) (hematoxylin-eosin, original magnification ×60). B, The posterior segment shows the annular cuticle (black arrow), holomyarian muscle coat, testis (arrowhead), and intestine (white arrow) (hematoxylin-eosin, original magnification ×120).*

Figure 3. *A, The colonic mucosa shows moderate chronic inflammation, mucosal architectural distortion, and focal histiocytic aggregates (arrow) (hematoxylin-eosin, original magnification ×250). B, The mucosal infiltrates include increased eosinophils (hematoxylin-eosin, original magnification ×500).*

the helminth exhibits specialized columnar epithelial cells termed a *bacillary band* that may participate in respiration. The posterior portion of the male trichurid shows an annular cuticle without striations, and includes the intestine and tubular reproductive organs that were evident in the present case. The posterior segment of the female trichurid includes a nonannulated cuticle, and the body cavity contains a tubular vulva, vagina, uterus, oviduct, ovaries, and seminal receptacle. Eggs with brown-tinged shells and prominent bipolar plugs may be identified within the female genital tract. Of note, female worms were not identified in the biopsy specimens of the present case.

Trichuris suis reportedly does not mature to an egg-laying stage in man, and reportedly dies several weeks following implantation.[2] In this case, immature helminths were identified in the ileocecal region. Their stichosomal apparatus was small and there was no direct evidence of growth into the bowel lumen. However, the presence of an adult male in the cecum indicates that maturation to the sexual stage of *T suis* does occur in man. In the present case, the single coiled male organism was identified free-floating in the lumen, without evidence of mucosal attachment; it may have been in the midst of being expelled from the bowel.

Nematode helminths evade destruction by host immune responses by a variety of mechanisms, including the absorption of host proteins onto the superficial cuticle.[3] Elimination of parasites by the host is mediated by the T helper subtype 2 (T_H2) inflammatory response. Expulsion of *Trichuris muris* in experimental models requires the participation of interleukin (IL)-1α, IL-1β,[4] IL-4, IL-9, and IL-13 to polarize the T-helper response.[5] Activation of NF-κ B1 and B2 is also necessary to mount a T_H2 response to *Trichuris* infection.[6] *Trichuris* participates in the interaction with the T_H2 pathway by virtue of its expression of IL-4 and IL-13 receptors[7] and via the release of a secretory chymotrypsin/elastase inhibitor[8] that may play a role in immunomodulation.

The role of iatrogenic helminthic infection as an immunomodulator is currently being investigated in the treatment of inflammatory bowel disease.[2,9,10] Inflammatory bowel disease, and especially Crohn disease, is characterized by the expression of T_H1 cytokines, including interferon-γ and tumor necrosis factor, that promote lymphohistiocytic inflammation and granuloma production within the bowel. Because a polarized T_H2 response can antagonize T_H1 pathways, investigators have explored the possibility that helminthic infection may inhibit T_H1 inflammation in vivo and have a salutary effect in these disorders.[11]

In the present case, the bowel mucosa at all sites, including those not actively infected by *T suis*, showed a lymphoplasmacytic infiltrate with substantial numbers of eosinophils, consistent with the development of a T_H2-mediated response. However, the biopsies also showed moderately active Crohn disease, and the patient reported no substantial improvement in symptoms.

Summers and coworkers[9,10] recently reported their experience with 7 patients, 4 with Crohn disease and 3 with ulcerative colitis, who were treated with swine trichurid ova. Patients received 2500 viable *Trichuris* ova orally and were monitored for the next 12 weeks for changes in their Crohn Disease Activity Index. Several patients received multiple doses of ova. None of the patients showed evidence of persistent *Trichuris* infection or new egg production. Three of the 4 patients with Crohn disease achieved remission, and the fourth patient showed a reduction in the Crohn Disease Activity Index. The patients with ulcerative colitis showed a mean reduction of 57% of the Crohn Disease Activity Index from baseline. However, the responses to a single dose were short-lived.

The findings in this case suggest that *T suis* ova can infect the human gastrointestinal tract and induce an inflammatory phenotype consistent with a T_H2 response. The absence of mature egg-laying females is consistent with the claim that maturation of *T suis* to egg-laying stages does not occur in vivo, but the presence of a sexually mature male trichurid begs the question as to whether productive infection may be possible.

In a recent communication, it was noted that *T suis* eggs recovered from human stool are viable and still potentially infectious.[12] Recently, a patient developed serious infection with *Campylobacter jejuni* and concomitant *T suis* ova in the stool.[13] The question has been raised as to whether investigators should actively take steps to eliminate residual *T suis* infection with antihelminthic therapy in patients who do not respond to this experimental mode of treatment.[14] As embryonic development of *Trichuris* eggs occurs ex vivo in soil, the risk of hyperinfection is reduced. Nevertheless, the present study does raise concerns as to whether persistent infection by sexually mature forms of *T suis* is possible in man.

In conclusion, pathologists should be aware of the possibility of iatrogenic *T suis* infection in patients with inflammatory bowel disease, as well as in patients who may pursue this mode of treatment off protocol for inflammatory bowel disease and other autoimmune disorders. Further studies will be necessary to determine the effectiveness of this mode of immunotherapy and whether this approach incurs the risk of clinically significant xenoinfection.

References

1. Marty A, Neafie R. Trichuriasis. In: Meyers W, Neafie RC, Marty AM, Wear DJ, eds. *Pathology of Infectious Diseases: Volume 1, Helminthiases.* Washington, DC: American Registry of Pathology, Armed Forces Institute of Pathology; 2000: 461–470.
2. Summers RW, Elliott DE, Qadir K, Urban JF, Thompson R, Weinstock JV. *Trichuris suis* seems to be safe and possibly effective in the treatment of inflammatory bowel disease. *Am J Gastroenterol.* 2003;98:2034–2041.
3. Boes J, Helwigh AB. Animal models of intestinal nematode infections of humans [review]. *Parasitology.* 2000;121(suppl):S97–111.
4. Helmby H, Grencis RK. Interleukin 1 plays a major role in the development of the TH2-mediated immunity. *Eur J Immunol.* 2004;34:3674–3681.
5. Deepe GS Jr, Smelt S, Louie JS. Tumor necrosis factor inhibition and opportunistic infections. *Clin Infect Dis.* 2005;41(suppl 3):S187–188.
6. Artis D, Shapira S, Mason N, et al. Differential requirement for NF-kappa B family members in control of helminth infection and intestinal inflammation. *J Immunol.* 2002;169:4481–4487.
7. Zarlenga DS, Dawson H, Kringel H, Solano-Aguilar G, Urban JF Jr. Molecular cloning of the swine IL-4 receptor alpha and IL-13 receptor 1-chains: effects of experimental *Toxoplasma gondii, Ascaris suum* and *Trichuris suis* infections on tissue mRNA levels. *Vet Immunol Immunopathol.* 2004;101:223–234.
8. Abner SR, Hill DE, Turner JR, et al. Response of intestinal epithelial cells to *Trichuris suis* excretory-secretory products and the influence on *Campylobacter jejuni* invasion under *in vitro* conditions. *J Parasitol.* 2002;88:738–745.
9. Summers RW, Elliott DE, Urban JF, Thompson RA, Weinstock JV. *Trichuris suis* therapy for active ulcerative colitis: a randomized controlled trial. *Gastroenterology.* 2005;128:825–832.
10. Summers RW, Elliott DE, Urban JF, Thompson RA, Weinstock JV. *Trichuris suis* therapy in Crohn's disease. *Gut.* 2005;54:87–90.
11. Radford-Smith GL. Will worms really cure Crohn's disease? *Gut.* 2005;54:6–8.
12. Beer R. The relationship between *Trichuris trichiura* (Linnaeus 1758) of man and *Trichuris suis* (Schrank 1788) of the pig. *Res Vet Sci.* 1976;20:47–54.
13. Shin JL, Gardiner GW, Deitel W, Kandel G. Does whipworm increase the pathogenicity of *Campylobacter jejuni*? *Can J Gastroenterol.* 2004;18:175–177.
14. Hsu S, Tseng P, Chen P. *Trichuris suis* therapy for ulcerative colitis: nonresponsive patients may need anti-helminth therapy. *Gastroenterology.* 2005;129: 768–769.