CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 38-2011: A 34-Year-Old Man with Diarrhea and Weakness

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PRESENTATION OF CASE

Dr. Andrew Courtwright (Medicine): A 34-year-old man was admitted to this hospital because of diarrhea and weakness.

Three days before admission, weakness developed in the patient's right hand, followed by increasing weakness in the left hand. During the next 2 days, weakness progressively involved the whole body, limiting the patient's ability to walk, and was associated with diffuse muscle pain, episodic vomiting, and multiple episodes of diarrhea. He became bedridden and required assistance with activities of daily living. He was brought to the emergency department at this hospital.

The patient had had diarrhea for 6 months, which had reportedly begun after he drank "dirty water" when snowbound in northern New England. Stools were foul-smelling and intermittently watery or soft, without blood or mucus, and were associated with transient midepigastric pain; stool frequency had increased since the onset of symptoms to up to 10 times per day. Episodes of nonbloody, nonbilious emesis had occurred once or twice daily for the previous month. He reported losing 27 kg of weight during that time, from his usual weight of 82 kg. He did not have fever, chills, night sweats, headache, chest pain, visual changes, shortness of breath, cough, urinary symptoms, numbness, or tingling. Four years earlier, he had had a prolonged period of recurrent diarrhea, which had resolved spontaneously and was not as severe as the present illness. He had fractured his arm in the past and his nose after a motor vehicle accident 5 months previously. He did not take any medications, had not sought medical attention for his illness because of religious beliefs, and had no known drug allergies. He was born in Brazil, had moved to the northeastern United States 8 years earlier, and lived with friends in coastal New England. He was sexually active with men and women, including a partner who was positive for the human immunodeficiency virus (HIV). The patient had a history of alcohol abuse and occasional illicit drug use (cocaine and marijuana); he reported stopping alcohol consumption 6 months earlier and stopping smoking 1.5 years before moving to the United States. He had consumed unpasteurized milk and dairy products and raw fish and meat approximately 6 months before presentation. There was no exposure to sick contacts or animals. He traveled in Brazil and the northeastern United States only.

It is not known when he last visited Brazil. Several relatives had had cancer; there was no family history of diarrheal illnesses.

On examination, the patient was alert and appeared ill and emaciated. The temperature was 36.6°C, the blood pressure 90/50 mm Hg, the pulse 148 beats per minute, the respiratory rate 24 breaths per minute, and the oxygen saturation 99% while he was breathing ambient air. The mucous membranes were dry. There was a grade 2/6 systolic ejection murmur. Bowel sounds were hyperactive, and the abdomen was soft, with suprapubic tenderness and no organomegaly or rebound. Grasp strength was 1 out of 5, and strength of the biceps, wrist and finger flexors and extensors, arm abductors, and leg muscles was 0 out of 5. Deep-tendon reflexes were absent, and the plantar reflexes were flexor; the remainder of the examination was normal. An electrocardiogram revealed supraventricular tachycardia with atrial and ventricular rates of 131 beats per minute, with diffuse, nonspecific ST-segment and T-wave abnormalities; the QT interval was 276 msec, with a QT interval corrected for heart rate (QTc) of 407 msec. Laboratory-test results are shown in Table 1. A stool specimen was guaiac-negative, and a chest radiograph was normal. Continuous cardiac monitoring was begun. Intravenous crystalloid and supplements of potassium chloride, magnesium sulfate, and sodium phosphate were administered; oral potassium chloride was also given. The patient was admitted to the medical intensive care unit (ICU), and oral intake was restricted to medications only. The level of serum thyrotropin was 6.7 μU per milliliter (reference range, 0.0 to 5.0) and free thyroxine 0.9 ng per deciliter (11.6 pmol per liter) (reference range, 0.9 to 1.8 ng per deciliter [11.6 to 23.2 pmol per liter]). Testing for hepatitis B and C viruses was negative, and levels of methemoglobin and carboxyhemoglobin were normal.

During the day of admission, laboratory tests were repeated every 2 to 3 hours; additional test results are shown in Table 1. Urinalysis revealed a pH of 6.0 (reference range, 5.0 to 9.0), 2+ occult blood, trace albumin, and mucin; it was otherwise normal. Radiographs of the abdomen showed a mild dilatation of the small bowel, probably representative of a small-bowel ileus, with a suggestion of free air in the right upper quadrant. Cumulative stool output was 1600 ml during the first 11 hours, and urine output was 1600 ml; cumulative intravenous and oral intake was 2900 ml.

On the morning of the second day, analysis of a stool specimen revealed a sodium level of 87 mmol per liter, a potassium level of 50.6 mmol per liter, osmolality of 271 mOsm per kilogram of water, and 33% fat (reference range, <20). The CD4+ T-cell count was 125 per cubic millimeter of blood.

A diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Edward T. Ryan: May we review the imaging studies?

Dr. Carmel G. Cronin: A plain-film radiograph of the abdomen obtained in the emergency department while the patient was in the supine position shows diffuse, mild small-bowel dilatation without a transition point. The large bowel is not dilated. These features may be consistent with an ileus. An extraluminal lucency in the right upper quadrant is worrisome for free air (Fig. 1A). Ideally, a plain-film radiograph would be performed, with the patient in an erect position, to confirm the presence of free air, but in this case the patient was too debilitated to stand. The spine and the sacroiliac joints appear normal. There are no gallstones or calcification in the pancreatic region.

With the patient in a supine position, a second abdominal radiograph obtained 2 days later shows similar findings of prominent small bowel and a suggestion of free air in the right upper quadrant. On the same day, a computed tomographic (CT) scan of the abdomen was obtained, which shows prominent small bowel, filled with gas and fluid, without a focal obstructing lesion, features consistent with an ileus. The large bowel is not dilated. There is no free air (Fig. 1B). A chest radiograph taken with the patient in the supine position was normal.

Dr. Ryan: This 34-year-old man presented with weakness to the point of paralysis. The patient reported no numbness or tingling; however, he reported muscle pain, and deep-tendon reflexes were absent. Initial considerations in the emergency department should have included severe peripheral neuropathy (e.g., the Guillain–Barré syndrome), drug effects, intoxication, and neuromuscular conditions such as the Lambert–Eaton myasthenic syndrome. Although paresthesias of hands and

feet are common in patients with the Guillain–Barré syndrome, diffuse muscle pain would be atypical. This patient was emaciated and reported chronic diarrhea of at least 6 months' duration, with up to 10 voluminous bowel movements a day, resulting in the loss of more than 30% of his body weight. It is important to determine whether the weakness and paralysis are direct manifestations of an intestinal infection. Although there are examples of intestinal infections with neurologic manifestations (Table 2), none of the classic pathogens seem likely in this case. I suspect that the most likely cause of this patient's weakness is malabsorption and electrolyte loss due to chronic diarrhea.

CHRONIC DIARRHEA

Further evaluation of this case should be focused on elucidating the nature of the chronic diarrhea. Is the intestinal process inflammatory or noninflammatory? We are told that the patient had no history of fever and that there was no blood in the stool, features that would strongly suggest a noninflammatory intestinal process. Noninflammatory diarrhea can be categorized as secretory or osmotic, and the stool osmolality of 271 mOsm

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	On Admission	11 Hr after Admission
Hematocrit (%)	41.0–53.0 (men)	40.0	31.5
White-cell count (per mm^3)	4500–11,000	18,000	22,600
Differential count (%)			
Neutrophils	40–70	87	86
Band forms	0–10	2	0
Lymphocytes	22–44	7	9
Monocytes	4–11	4	4
Eosinophils	0–8	0	1
Platelet count (per mm^3)	150,000–400,000	485,000	445,000
Smear description		Anisocytosis 1+, polychromatocytosis 1+, spherocytosis 1+, Howell–Jolly bodies present	Anisocytosis 1+, toxic granulations present
Activated partial-thromboplastin time (sec)	21.0–33.0		31.3
Prothrombin time (sec)	10.8–13.4	13.4	13.6
International normalized ratio		1.1	1.1
Sodium (mmol/liter)	135–145	133	144
Potassium (mmol/liter)	3.4–4.8	1.2	<1.5
Chloride (mmol/liter)	100–108	104	122
Carbon dioxide (mmol/liter)	23.0–31.9	13.9	12.6
Urea nitrogen (mg/dl)	8–25	22	19
Creatinine (mg/dl)	0.60–1.50	1.50	1.22
Estimated glomerular filtration rate (ml/min/1.73 m^2)	≥60	57	>60
Glucose (mg/dl)	70–110	105	85
Protein (g/dl)			
Total	6.0–8.3	8.2	6.7
Albumin	3.3–5.0	3.9	3.2
Globulin	2.6–4.1	4.3	3.5

Table 1. (Continued.)

Variable	Reference Range, Adults†	On Admission	11 Hr after Admission
Phosphorus (mg/dl)	2.6–4.5	1.5	0.7
Magnesium (mmol/liter)	0.7–1.0	0.8	1.3
Calcium (mg/dl)	8.5–10.5	9.3	8.1
Ionized calcium (mmol/liter)	1.14–1.30	1.34	
Alkaline phosphatase (U/liter)	45–115	126	102
Aspartate aminotransferase (U/liter)	10–40	64	50
Alanine aminotransferase (U/liter)	10–55	98	77
Creatine kinase (U/liter)	60–400 (men)	231	
Creatine kinase MB isoenzymes (ng/ml)	0.0–6.9	8.3	
Troponin I	Negative	Negative	
Troponin T (ng/ml)	<0.03	0.06	
Venous blood gas (while breathing ambient air)			
pH	7.30–7.40	7.21	7.23
Partial pressure of oxygen (mm Hg)	35–50	38	43
Partial pressure of carbon dioxide (mm Hg)	38–50	36	32
Base excess (mmol/liter)		12.6, negative	13.6, negative

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for magnesium to milligrams per deciliter, divide by 0.4114. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for ionized calcium to millimoles per liter, divide by 0.250.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

per kilogram of water would be consistent with a secretory process.[1] This patient also has a number of features that are consistent with malabsorption, including 33% fecal fat (normal range, <20%), anemia with thrombocytosis (suggesting iron deficiency), an elevated prothrombin time (suggesting vitamin K deficiency), a low-normal serum albumin level (consistent with protein loss or poor synthesis), and low total blood calcium and phosphorus levels. These features would be consistent with malabsorption of fat, vitamins, and micronutrients. Carbohydrate malabsorption may also be present; however, the most striking laboratory abnormality is severe hypokalemia.

HYPOKALEMIA

Hypokalemia may be due to poor intake; excessive losses through the intestine, kidneys, or skin; and redistribution of potassium stores to the intracellular environment. This patient's hypokalemia was probably multifactorial. He was losing potassium through his diarrhea and vomiting, he was perhaps losing potassium in his urine in the context of vomiting-associated bicarbonate loss and volume contraction, and he probably had poor intake because of recurrent vomiting. Hypokalemia (and hyperkalemia) can be associated with neuromuscular features ranging from weakness and muscle cramping to full paralysis[2-4]; the mechanism of action is thought to be due to potassium-related alterations of nerve action potentials. Clinical features include weakness, ileus, electrocardiographic changes, and myopathy. Periodic hypokalemic paralysis should be considered in this patient; however, the chronic nature of his illness would argue against this entity.[3,5]

INTESTINAL DISORDERS THAT CAUSE HYPOKALEMIA

What are the most likely intestinal processes that could result in hypokalemia-associated paralysis

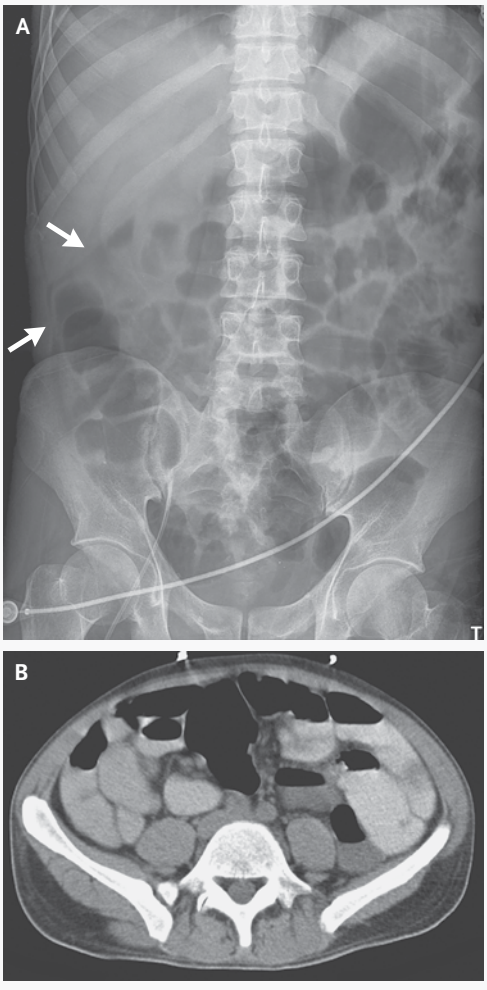

Figure 1. Abdominal Imaging.

A plain-film radiograph of the abdomen obtained with the patient in the supine position shows diffuse, mild small-bowel dilatation without a transition point. The large bowel is not dilated. These features are suggestive of an ileus. In the right upper quadrant, there is extraluminal lucency that is suggestive of free air (Panel A, arrows). The spine and the sacroiliac joints appear normal. No gallstones and no calcification can be seen in the pancreatic region. An abdominal CT scan obtained 2 days later (Panel B) shows prominent small bowel filled with gas and fluid, without a focal obstructing lesion. The large bowel is not dilated. There is no free air. These features are consistent with a small-bowel ileus.

in a patient with chronic, emaciating, voluminous, secretory, malabsorption diarrhea? Many infectious and noninfectious entities can cause chronic diarrhea (Table 3).[6] The lack of inflammatory markers would argue against inflammatory bowel disease. Short-bowel syndrome would be unlikely in the absence of previous abdominal surgery. Neuroendocrine tumors may present in a similar manner, but they are relatively rare. The diarrhea associated with laxative abuse is usually osmotic. Celiac disease is not usually as severe as this patient's illness. Although pancreatic insufficiency can present with a chronic malabsorptive diarrhea, the patient has no previous history of severe pancreatitis, there are no calcifications on abdominal imaging of the pancreatic bed, and the patient does not have diabetes, although endocrine and exocrine function can be disparate. The degree of illness in this patient would be highly atypical for lactose intolerance as a single diagnosis. Similarly, the onset of tropical sprue 8 years after immigrating to the United States would be highly unusual.

There are no clinical features suggestive of motility disorders or syndromes associated with the malabsorption of bile salts, and Brainerd's diarrhea, an entity of undetermined cause, has classically been defined in epidemic situations. Postinfectious enteropathy and irritable bowel syndrome are possible, but we are not given a history of an inciting event, and the voluminous nature of the diarrhea with an absence of severe cramping and alternating periods of constipation make this unlikely. Microscopic colitis can present with a chronic secretory diarrhea, but malabsorption would be rare.[7] Another entity to at least consider in a patient with diarrhea and neurologic changes would be pellagra due to niacin deficiency, but the peripheral neuropathy and absence of a classic dermatitis effectively rule out that diagnosis.[8]

Infectious causes of chronic diarrhea are usually protozoal, although bacterial overgrowth of the small intestine should be considered, as should chronic *Clostridium difficile* colitis and campylobacteriosis, but the absence of blood and inflammatory markers in the stool strongly argue against these latter diagnoses. Infection with microsporidia can result in chronic diarrhea, although usually in persons who have advanced acquired immunodeficiency syndrome (AIDS) or who are severely immunocompromised with other cell-mediated deficiencies.[9] Similarly, chronic intestinal cryptosporidiosis, leishmaniasis, and cystoisosporiasis (formerly known as isosporiasis) could also result in a wasting illness and chronic diarrheal process, but this patient's degree of illness would usually be seen in persons with compromised cellular immunity, such as those with ad-

Table 2. Intestinal Infections and Neurologic, Neuromuscular, or Muscular Syndromes.

Agent	Neurologic Manifestation	Comment
Enteroviruses		
Polio	Paralytic motor symptoms, meningitis, encephalitis	Diarrhea not present at time of neurologic syndrome
Enterovirus 71		
Bacteria		
Campylobacter jejuni	Guillain–Barré syndrome	Postinfectious, inflammatory, demyelinating; diarrhea at time of neurologic syndrome atypical
Yersinia enterocolitica		
Shigella species		
Salmonella species		
Listeria monocytogenes	Meningoencephalitis	Most commonly affects neonates, pregnant women, the elderly, and immunocompromised persons; diarrhea at time of neurologic syndrome is not seen
Tropheryma whipplei (Whipple's disease)	Encephalitis, ocular abnormalities	Classic manifestations include arthritis, diarrhea, neurologic syndromes, rash
Protozoa		
Toxoplasma gondii	Myositis	Diarrhea not a feature
Sarcocystis species	Myositis	Eosinophilia may be present
Helminths		
Trichinella spiralis	Myositis, cardiomyositis	Diarrhea present in first stage of infection, followed by myositis; eosinophilia common

vanced HIV infection,[10] although *Cystoisospora belli* (also known as *Isospora belli*) infection can cause chronic diarrhea in immunocompetent persons. However, in immunocompetent persons with chronic cystoisosporiasis, peripheral eosinophilia is often present, a feature that this patient does not have. Intestinal amebiasis and balantidiasis can also cause chronic diarrhea, but the absence of blood in the stool or intestinal markers of inflammation in this patient argue against these diagnoses. Chronic giardiasis caused by *Giardia lamblia* should be seriously considered in this patient, since it can cause chronic secretory diarrhea with malabsorption and does not require an underlying immunocompromised state.[11]

Which of these is the most likely diagnosis in this patient? A fundamental question is whether we think he is severely immunocompromised, in particular with an immunodeficiency affecting cellular immunity, such as that seen in chronic HIV type 1 (HIV-1) infection. We know that he has a very low CD4+ T-cell count, has had sexual encounters with an HIV-positive person, has an emaciating chronic illness, and was admitted with a moderately elevated serum globulin level. All these features are consistent with advanced HIV-1 infection. However, a peripheral white-cell count of 18,000 to 22,600 per cubic millimeter and a platelet count of 485,000 per cubic millimeter are somewhat atypical in persons with advanced HIV infection.

Therefore, I would consider two approaches in generating a final differential diagnosis. Although a number of intestinal infections have been associated with hypokalemic paralysis, including giardia, salmonella, yersinia, strongyloides, and cystoisospora,[12-16] if the patient does not have HIV infection, I think the most likely diagnosis is giardiasis. However, giardiasis of this severity would suggest an underlying immunoglobulin deficiency, since hypogammaglobulinemia is associated with severe, recalcitrant, and relapsing giardiasis.[17] An absence of previous head and neck or airway infection argues against an IgA deficiency, and the elevated serum globulin level argues against panhypogammaglobulinemia.

If this patient is infected with HIV, I think the leading diagnoses would be intestinal cryptosporidiosis, cystoisosporiasis, leishmaniasis, or microsporidiosis. All these intestinal infections can result in severe and chronic intestinal diarrheal processes. Of these, cystoisosporiasis has been associated with hypokalemic paralysis in an HIV-infected person.[16]

We are left with the reality that none of these infections are classically associated with peripheral leukocytosis or thrombocytosis, features present in this case. The thrombocytosis may reflect a chronic infection, inflammatory state, and perhaps iron-deficiency anemia. The leukocytosis may reflect a tiny intestinal perforation that could be associated with the severe ileus and could be suggested by the radiographic finding of possible free intraperitoneal air. Although intestinal perforation is not a

Table 3. Causes of Chronic Diarrhea.

Type	Comment
Infectious	
Viral	
Cytomegalovirus	Occurs in severely cellularly immunocompromised persons; most commonly involves esophagus and colon; diarrhea is usually bloody
Herpes simplex virus	Manifested as proctitis or colitis, usually in cellularly immunocompromised persons
HIV enteropathy	Unclear mechanism
Bacterial	
Bacterial overgrowth of small intestine	May present as malabsorption syndrome
Clostridium difficile	Diarrhea usually bloody or inflammatory; peripheral leukocytosis may be prominent
Campylobacter jejuni	May be chronic; diarrhea usually bloody or inflammatory
Tropheryma whipplei (Whipple's disease)	Classic manifestations include arthritis, diarrhea, neurologic syndromes, rash
Mycobacteria (*Mycobacterium tuberculosis*, *M. avium* complex)	May be diffusely infiltrative; if localized to ileal area, can impede bile-salt reabsorption; intestinal *M. avium* complex can be present in severely cellularly immunocompromised persons
Fungal	
Histoplasma capsulatum, Paracoccidioides brasiliensis, Cryptococcus neoformans, others	Intestinal fungal infections may be associated with oral or nasopharyngeal ulcers; intestinal involvement may be diffusely infiltrative, but if localized to ileal area, can impede bile-salt reabsorption; more severe in immunocompromised persons
Protozoal	
Microsporidial (e.g., *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*)	Occurs in severely cellularly immunocompromised persons; may be systemic
Kinetoplastida	
Leishmania species	Occurs in severely cellularly immunocompromised persons
Flagellates	
Giardia lamblia	Secretory; malabsorption syndrome may occur; universal infection
Coccidial	
Cryptosporidium hominis, C. parvum	May be prolonged, severe, and life-threatening in cellularly immunocompromised persons
Cyclospora cayetanensis	Usually resolves in 1 to 4 wk
Cystoisospora belli	May be severe in cellularly immunocompromised persons; very rarely can cause chronic infection in apparently immunocompetent persons (in whom peripheral eosinophilia may be present)
Amebic	
Entamoeba histolytica	Diarrhea usually contains blood
E. polecki	Diarrhea usually contains blood; rare, associated with pig and monkey exposure

Table 3. (Continued.)

Type	Comment
Ciliates	
Balantidium coli	Diarrhea usually contains blood; rare, associated with pig exposure
Helminthic	Intestinal helminthic infections are associated with intestinal irregularities, but they are usually not common causes of chronic voluminous diarrhea
Schistosoma species	Chronic intestinal inflammation, polyps, and ileal masses may be associated with diarrhea; eosinophilia may be present
Noninfectious	
Inflammatory bowel disease	Stool is classically inflammatory or bloody
Celiac disease (e.g., gluten-sensitive enteropathy, nontropical sprue)	Resolves with removal of gluten from diet
Postinfectious enteropathy or irritable bowel syndrome	Classically associated with periods of diarrhea alternating with constipation
Lactase deficiency	May compound other enteropathies
Pancreatic insufficiency	May be associated with ethanol abuse and chronic pancreatitis
Motility disorders	Diabetic neuropathy
Ischemia	Abdominal pain may be prominent; blood in stool
Neuroendocrine tumors	Carcinoid, vasoactive intestinal peptide–secreting tumors, and others
Villous adenoma	
Infiltrative mucosal process	Intestinal lymphoma, mycobacteria, and others
Intestinal Kaposi's sarcoma	Advanced HIV infection, stool bloody
Bile-salt malabsorption	Including ileal disorder impeding bile-salt absorption
Short-bowel syndrome	Usually history of surgery
Laxative abuse	Osmotic diarrhea
Vitamin deficiency (e.g., pellagra [niacin deficiency])	Diarrhea, dementia, dermatitis
Microscopic colitis	Chronic secretory diarrhea (malabsorption rare)
Tropical sprue	Malabsorption syndrome
Brainerd's diarrhea	Unknown cause; epidemic chronic diarrhea

typical feature of any of these infections, there is one case report of intestinal perforation in an HIV-infected patient with microsporidiosis.[18]

SUMMARY

In summary, I believe that this patient has hypokalemia-associated paralysis due to a chronic intestinal protozoal or microsporidial infection — either severe giardiasis if he is not infected with HIV and has a deficiency in an immunoglobulin subtype, or intestinal cystoisosporiasis, cryptosporidiosis, microsporidiosis, or leishmaniasis if he is HIV-infected. All these infections can result in severe and chronic intestinal diarrheal processes. Cystoisospora has been associated with hypokalemic paralysis in an HIV-infected person,[16] so it would possibly be the leading choice if this patient is HIV-infected. How should we proceed?

Because of the possibility of an intestinal perforation, I would recommend initiating broad-spectrum antibiotics, including metronidazole. I would replenish potassium parenterally and minimize oral food intake to minimize insulin secretion in the short-term and avoid exacerbation of potassium shifts. I would also replenish other electrolytes, including magnesium, and would hydrate the patient and monitor him carefully.

To make a diagnosis, I would test for anti-HIV antibodies. I would also examine a stool specimen for ova and parasites, using acid-fast stains, trichrome stain, and immunofluorescence assays for intestinal protozoa and microsporidia and

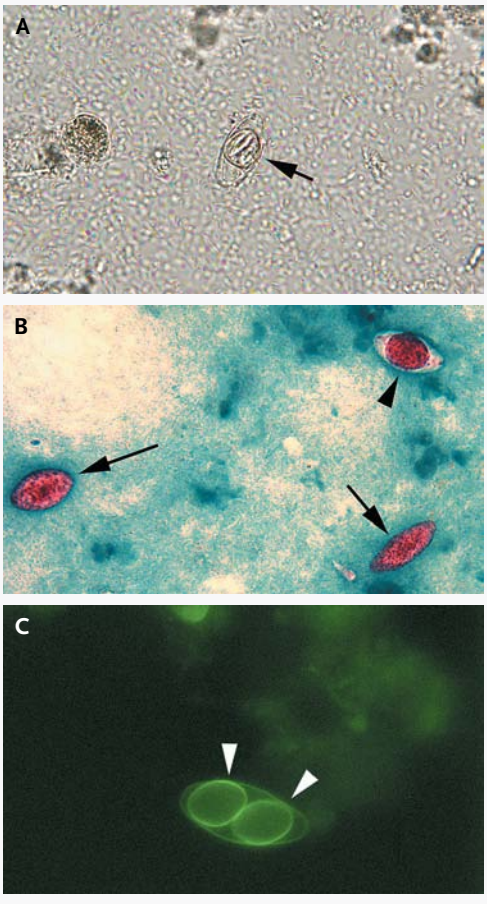

Figure 2. Stool Studies.

Cystoisospora belli oocysts were detected in an unstained wet mount prepared after concentration of the stool specimen by the formalin–ethyl acetate technique (Panel A, arrow) and in a fecal smear stained by Kinyoun's modified acid-fast staining method (Panel B). Cystoisospora oocysts are thin-walled and ellipsoidal and range from 20 to 33 μm in length and from 10 to 19 μm in width.[19] Oocysts are immature (unsporulated) when found in freshly passed feces and may contain a single, spherical sporoblast (arrowhead) or may lack a distinct sporoblast (arrows).[19] After a few days of room-temperature incubation, the oocysts mature to sporulated oocysts containing two sporocysts (Panel C, arrowheads). Oocysts will show autofluorescence when wet mounts are examined by fluorescence microscopy, making detection easier.

antigen-detection assays for giardia and cryptosporidia. If these tests are unrevealing, I would repeat the stool studies and perform additional serologic assays, including assessment for anti-gliadin antibodies. If the workup is again unrevealing, I would proceed to additional imaging and endoscopy after clinical stabilization of the patient.

Dr. Eric S. Rosenberg (Pathology): Dr. Courtwright, would you give us your initial clinical impression of this patient?

Dr. Courtwright: In view of the patient's history and clinical presentation, we thought he might have advanced HIV infection; therefore, we favored a diagnosis of chronic diarrhea with infectious causes, particularly microsporidia, cystoisospora, cryptosporidia, giardia, and *Entamoeba histolytica*.

CLINICAL DIAGNOSIS

Chronic diarrhea, mostly likely due to an intestinal parasite.

DR. EDWARD T. RYAN'S DIAGNOSIS

Hypokalemia-associated paralysis due to a chronic intestinal protozoal infection.

PATHOLOGICAL DISCUSSION

Dr. John A. Branda: Testing for HIV infection was performed on admission to this hospital. An enzyme immunoassay was positive for antibodies against HIV-1 or HIV-2. A Western blot analysis for HIV-1 was also positive and revealed a mature antibody response. This confirmed the diagnosis of HIV-1 infection. In addition, testing for HIV RNA revealed a viral load of 334,000 copies per milliliter of plasma, independently verifying the diagnosis.

A stool specimen collected on hospital day 2 was examined for ova and parasites and revealed the cause of the patient's protracted diarrhea. *C. belli* oocysts were detected in a wet preparation after the stool specimen had been concentrated with the use of the formalin–ethyl acetate technique (Fig. 2A). The finding was confirmed by examination of a smear treated with a modified acid-fast stain (Fig. 2B), which highlights the oocysts, and by observation of the correct morphologic features after oocyst maturation in a potassium dichromate solution (Fig. 2C).

Cystoisospora is distributed worldwide, but infections are most common in tropical and subtropical areas (www.dpd.cdc.gov/dpdx/html/cystoisosporiasis.htm). It is acquired through the fecal–oral route. Although our patient reported consuming "dirty water" before the onset of di-

arrhea, this exposure took place in northern New England, a region in which the organism is uncommon. It is more likely that the infection was acquired during a visit to his native Brazil; it is not known how recently the patient had traveled there. One could also consider the possibility that infection was acquired before immigration and reactivated after immunosuppression. Recurrence of latent infection has been proposed as one possible explanation for the higher prevalence of cystoisospora among immigrants with AIDS than among U.S.-born persons with AIDS.[20] However, the organism infects principally the intestinal epithelium, which undergoes rapid turnover and is therefore unlikely to serve as a long-term reservoir for latent organisms.[20] Sexual transmission through oral–anal contact has also been suggested[21] but seems unlikely, since oocysts excreted in stool are usually immature and must exist outside the host for 1 or 2 days before becoming infective.

Dr. Rosenberg: Dr. Upshaw, would you tell us what happened with the patient?

Dr. Jenica N. Upshaw (Medicine): The patient was admitted to the medical ICU. Potassium was aggressively replenished, and his weakness resolved. He was initially treated with broad-spectrum antimicrobial agents, and once the results of the analysis of the stool for ova and parasites were available, treatment was narrowed to trimethoprim–sulfamethoxazole. The diarrhea decreased during the next 5 or 6 days, and he was then transferred out of the ICU. The hospital course was complicated by deep-vein thrombosis associated with a peripherally inserted central catheter, urinary tract infection with klebsiella species, and hospital-acquired pneumonia, but the patient eventually recovered and was discharged after 11 days in the hospital. He was followed by the infectious disease service while in the hospital, and the plan was to continue treatment with trimethoprim–sulfamethoxazole and to initiate HIV therapy on an outpatient basis during the next 2 weeks. Unfortunately, he did not come to his follow-up appointments. After multiple telephone calls, he said he did not want additional medical care. Because of his religious beliefs, he preferred to pursue alternative therapies.

Four months later, the patient was readmitted with fever, weakness in the right arm, and an expressive aphasia. He was found to have a ring-enhancing lesion in the basal ganglia on the left side and midline shift, presumably due to toxoplasmosis. After treatment for toxoplasmosis, the aphasia and weakness improved. After discharge, antiretroviral therapy was initiated. At the last follow-up, the patient was taking his medicine and his CD4+ T-cell count was 233 per cubic millimeter.

Dr. Hasan Bazari (Medicine): The degree of ileus was quite prominent; do you think it can be ascribed only to the intestinal infection, or was it a component of the hypokalemia?

Dr. Ryan: I suspect the ileus was caused mainly by profound hypokalemia.

PATHOLOGICAL DIAGNOSIS

Cystoisospora belli enteritis and HIV infection.

Dr. Branda reports receiving grant support from DiaSorin. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

REFERENCES

1. Eherer AJ, Fordtran JS. Fecal osmotic gap and pH in experimental diarrhea of various causes. Gastroenterology 1992;103:545-51.
2. Lin SH. Thyrotoxic periodic paralysis. Mayo Clin Proc 2005;80:99-105.
3. Lin SH, Davids MR, Halperin ML. Hypokalaemia and paralysis. QJM 2003;96:161-9.
4. Stedwell RE, Allen KM, Binder LS. Hypokalemic paralyses: a review of the etiologies, pathophysiology, presentation, and therapy. Am J Emerg Med 1992;10:143-8.
5. Jurkat-Rott K, Lehmann-Horn F. Paroxysmal muscle weakness: the familial periodic paralyses. J Neurol 2006;253:1391-8.
6. Pawlowski SW, Warren CA, Guerrant R. Diagnosis and treatment of acute or persistent diarrhea. Gastroenterology 2009;136:1874-86.
7. Tangri V, Chande N. Microscopic colitis: an update. J Clin Gastroenterol 2009;43:293-6.
8. Hegyi J, Schwartz RA, Hegyi V. Pellagra: dermatitis, dementia, and diarrhea. Int J Dermatol 2004;43:1-5.
9. Didier ES. Microsporidiosis: an emerging and opportunistic infection in humans and animals. Acta Trop 2005;94:61-76.
10. Lewthwaite P, Gill GV, Hart CA, Beeching NJ. Gastrointestinal parasites in the immunocompromised. Curr Opin Infect Dis 2005;18:427-35.
11. Huang DB, White AC. An updated review on Cryptosporidium and Giardia. Gastroenterol Clin North Am 2006;35:291-314.
12. Cervelló A, Alfaro A, Chumillas MJ. Hypokalemic myopathy induced by Giardia lamblia. N Engl J Med 1993;329:210-1. [Erratum, N Engl J Med 1993;329:1139.]
13. da Silva OA, Amaral CF, da Silveira JC, Lopez M, Pittella JE. Hypokalemic respiratory muscle paralysis following Strongyloides stercoralis hyperinfection: a case report. Am J Trop Med Hyg 1981;30:69-73.
14. Orman RA, Lewis JB Jr. Flaccid quadriparesis associated with Yersinia enterocolitis-induced hypokalemia. Arch Intern Med 1989;149:1193-4.

15. Reid AC, Draper IT. Flaccid quadriparesis due to Salmonella enteritis. Scott Med J 1980;25:129-30.
16. Williams DT, Smith RS, Mallon WK. Severe hypokalemia, paralysis, and AIDS-associated Isospora Belli diarrhea. J Emerg Med 2008 November 6 (Epub ahead of print).
17. Oksenhendler E, Gérard L, Fieschi C, et al. Infections in 252 patients with common variable immunodeficiency. Clin Infect Dis 2008;46:1547-54.
18. Soule JB, Halverson AL, Becker RB, Pistole MC, Orenstein JM. A patient with acquired immunodeficiency syndrome and untreated Encephalitozoon (Septata) intestinalis microsporidiosis leading to small bowel perforation: response to albendazole. Arch Pathol Lab Med 1997;121:880-7.
19. Ash LR, Orihel T. Atlas of human parasitology. 5th ed. Chicago: ASCP Press, 2007.
20. Sorvillo FJ, Lieb LE, Seidel J, Kerndt P, Turner J, Ash LR. Epidemiology of isosporiasis among persons with acquired immunodeficiency syndrome in Los Angeles County. Am J Trop Med Hyg 1995;53:656-9.
21. Forthal DN, Guest SS. Isospora belli enteritis in three homosexual men. Am J Trop Med Hyg 1984;33:1060-4.