CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 28-2014: A 39-Year-Old Man with a Rash, Headache, Fever, Nausea, and Photophobia

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PRESENTATION OF CASE

Dr. Mark B. Geyer (Medicine): A 39-year-old man was admitted to this hospital because of a severe headache, nausea, and photophobia.

The patient had been well until approximately 1 month before the current presentation, when a pruritic rash developed below the waist, most prominently on the left upper thigh. The rash was similar to transient rashes he had had in the past. Ten days before this presentation, he was seen in the urgent care clinic at this hospital for evaluation. On examination, there were pigment changes on the face and lower abdomen, scattered small papules involving the lower legs and wrists, purpura on the left thigh, and multiple scattered excoriations. A diagnosis of dermatitis was made, and he was referred to the dermatology clinic. On evaluation at the dermatology clinic the next day, he reported severe itching, including on his ears. He had not used any new soaps or detergents. On examination, there were geometric erythematous-to-violaceous patches and plaques, most notably on the abdomen under the belt buckle and on both legs in the location of the pants pockets, with depigmentation and prurigo nodules, and there was a low density of brown papules (2 to 4 mm in diameter) over the trunk and limbs that were consistent with benign nevi. The remainder of the examination was normal. A diagnosis of severe contact dermatitis was made and was thought to be caused by coins or nickel on his clothing. A tapered course of prednisone was administered.

Nine days later, at 4 p.m. on the day of admission, a headache developed in the patient that was unlike any pain he had had previously and that was associated with increasing agitation and restlessness. He self-administered ibuprofen, without improvement. He was brought to the emergency department at this hospital by his family.

The history was obtained from the patient and his relatives. He rated his pain at 10 on a scale of 0 to 10 (with 10 indicating the most severe pain). He reported photophobia and nausea, with no fever, neck stiffness, vomiting, cough, dyspnea, head trauma, or chest or abdominal pain. He had melasma and acne; he had had hidradenitis suppurativa and, during the previous 8 years, recurrent pruritic rashes predominantly around the waist and axillae that were associated with transient eosinophilia (910 cells per cubic millimeter [16%]; reference range, 100 to 300). Four years earlier, the patient had had a partial small-bowel obstruction and un-

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derwent resection of a Meckel's diverticulum. Medications included prednisone and hydroxyzine hydrochloride, as needed for itching. He had no known allergies to medications. Vaccination history was not known. He was born in the Dominican Republic, had immigrated to the United States more than 15 years earlier, lived with his wife and children, and worked indoors in a service capacity. He spoke Spanish as his primary language. He drank alcohol rarely and did not smoke or use illicit drugs. He had visited the Dominican Republic 2 months before these symptoms occurred.

On examination, the patient was oriented to person, place, and time and was agitated and tearful, holding his head, and moaning. The temperature was 36.7°C to 38.1°C, the pulse 153 beats per minute, the respiratory rate 28 breaths per minute, and the oxygen saturation 100% while he was breathing ambient air. The mucous membranes were dry. The pupils were 4 mm in diameter and briskly reactive to light. The neck was stiff, with pain on flexion and rotation. Strength was 4/5 bilaterally, the gait was unsteady, and he was unable to stand without assistance. The remainder of the examination was normal. The hematocrit, hemoglobin level, platelet count, and results of liver- and renal-function tests were normal, as were blood levels of total protein, albumin, globulin, and calcium; other test results are shown in Table 1. Computed tomography of the head, performed without the administration of contrast material, revealed no evidence of acute intracranial hemorrhage, territorial infarction, or intracranial mass lesion. A chest radiograph was normal. Blood specimens were cultured. An electrocardiogram showed sinus rhythm at a rate of 132 beats per minute and was otherwise normal.

Lumbar puncture was performed. Results of the cerebrospinal fluid (CSF) analysis are shown in Table 1. Gram's staining of the CSF revealed abundant polymorphonuclear leukocytes and very few gram-positive cocci in pairs. Ceftriaxone, vancomycin, acyclovir, magnesium, and metoclopramide were administered intravenously. The patient was admitted to the hospital. Rifampin, ondansetron, dexamethasone, and a narcotic analgesic agent were added, and acyclovir was stopped. During the first hospital day, fevers and chills resolved but headache and neck stiffness persisted. Diagnostic tests were performed.

DIFFERENTIAL DIAGNOSIS

Dr. Read Pukkila-Worley: On presentation to this hospital, this 39-year-old man was critically ill with presumed bacterial meningitis, which requires prompt diagnosis and treatment. It is therefore appropriate to focus initially on this problem, in the hope of establishing a unifying diagnosis that explains the numerous features of this case.

ACUTE BACTERIAL MENINGITIS

The patient had abrupt onset of fever and neck stiffness, classic symptoms of acute bacterial meningitis that are found on initial physical examination in 95% and 88% of cases, respectively.[1] Moreover, CSF analysis revealed findings typical for bacterial meningitis, including a markedly elevated white-cell count (13,800 per cubic millimeter) with 90% neutrophils, hypoglycorrhachia (a low CSF glucose level), an abnormally elevated total protein level, and very few gram-positive cocci in pairs. Indeed, a white-cell count of more than 2000 per cubic millimeter or the presence of more than 1180 neutrophils per cubic millimeter in the CSF is nearly 100% specific for the diagnosis of bacterial meningitis,[2,3] as is the finding of bacteria on Gram's staining of the CSF.[4] We can therefore focus our differential diagnosis on the gram-positive cocci that cause acute bacterial meningitis.

The most common cause of bacterial meningitis in the United States is *Streptococcus pneumoniae*, a gram-positive coccus that is responsible for 58% of all cases.[5] Although the patient's presentation is compatible with pneumococcal meningitis, there are features of this case that do not support this diagnosis. First, patients with *Strep. pneumoniae*–associated meningitis often have a concurrent pneumococcal infection outside the central nervous system, such as pneumonia, endocarditis, otitis media, mastoiditis, or sinusitis.[4] A prodrome associated with one of these infections was not evident in this patient. In addition, the appearance of *Strep. pneumoniae* on Gram's staining is classically described as lancet-shaped gram-positive diplococci, which is slightly different from what was seen in this case. However, because of the potential severity of pneumococcal meningitis, empirical treatment directed toward both penicillin-susceptible and

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	On Admission
Blood		
White-cell count (per mm³)	4500–11,000	17,400
Differential count (%)		
Neutrophils	40–70	86.9
Lymphocytes	22–44	8.5
Monocytes	4–11	1.9
Eosinophils	0–8	2.1
Basophils	0–3	0.2
Sodium (mmol/liter)	135–145	134
Potassium (mmol/liter)	3.4–4.8	3.9
Chloride (mmol/liter)	100–108	93
Carbon dioxide (mmol/liter)	23.0–31.9	25.5
Anion gap (mmol/liter)	3–15	16
Glucose (mg/dl)	70–110	121
Phosphorus (mg/dl)	2.6–4.5	1.4
Magnesium (mg/dl)	1.7–2.4	1.5
Lactic acid (mmol/liter)	0.5–2.2	3.8
Cerebrospinal fluid		
Opening pressure (cm of water)		Unable to obtain with patient in upright position
Color	Colorless	Colorless
Turbidity	Clear	Moderate
Xanthochromia	None	None
Red-cell count (per mm³)		
Tube 1	None	11
Tube 4	None	12
Count of white cells and other nucleated cells (per mm³)		
Tube 1	0–5	13,800
Tube 4	0–5	13,150
Differential count (tube 1 of 4) (%)		
Neutrophils	0	90
Band forms	0	3
Lymphocytes	Not defined	4
Monocytes	Not defined	3
Protein (mg/dl)	5–55	195
Glucose (mg/dl)	50–75	46

* 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 millimoles per liter, multiply by 0.4114. To convert the values for lactic acid to milligrams per deciliter, divide by 0.1110.

† 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.

penicillin-resistant strains of *Strep. pneumoniae* is certainly appropriate while more diagnostic information is gathered.

Strep. agalactiae (group B streptococcus) is an important cause of neonatal sepsis and can occasionally cause acute bacterial meningitis in adults.[6] Risk factors for group B streptococcal meningitis in adults include coexisting illnesses and the antecedent administration of glucocorticoids,[7,8] which this patient had received. The gram-positive organisms *Staphylococcus aureus* and enterococcus species can cause bacterial meningitis after neurosurgery but are uncommon agents of meningitis in the absence of immunosuppression or foci of infection outside the central nervous system.[9-11] Similarly, *Strep. salivarius*–associated meningitis has been reported after spinal anesthesia[12] and myelogram procedures,[13] and meningitis can occur as a consequence of *Staph. epidermidis* infection of central nervous system shunts. None of these organisms seem likely given this patient's relatively unremarkable medical history. Other gram-positive bacterial pathogens that can cause meningitis are *Strep. bovis* (which can seed the meninges in persons with colonic disease),[14] *Strep. pyogenes* (a rare agent of meningitis, as a complication of severe otitis media, sinusitis, or pharyngitis),[15] *Strep. suis* (a common cause of meningitis in Vietnam but not in the United States),[16] and *Strep. viridans*.[17] The gram-positive bacillus *Listeria monocytogenes* is an important cause of bacterial meningitis and can occasionally be misidentified in clinical specimens as gram-positive cocci.[18]

Many of these pathogens are plausible causes of meningitis in this patient, but it is unclear why an infection of the central nervous system developed. Therefore, I will examine the other principal medical problems to search for a potential explanation.

RASHES

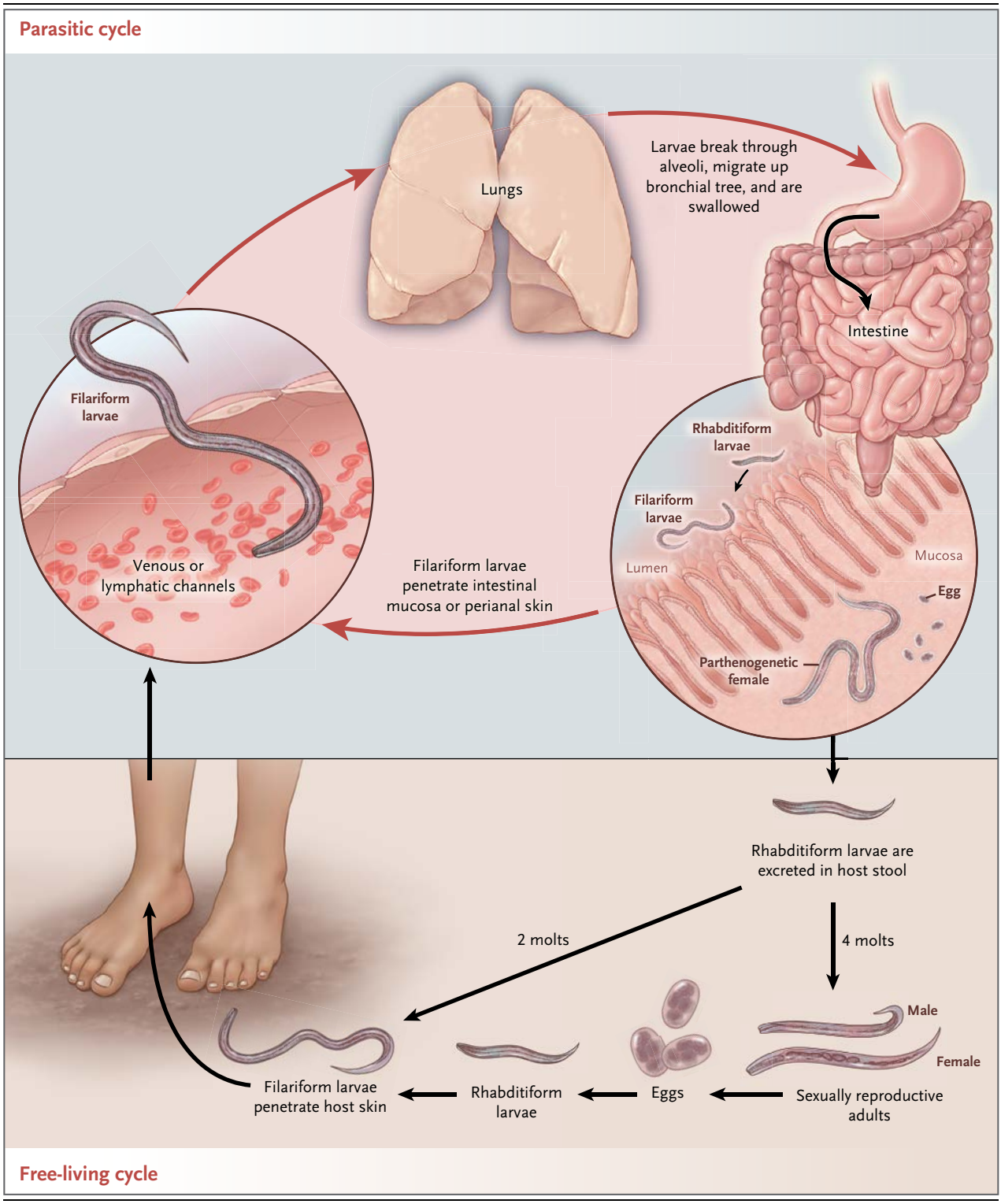
The patient had an 8-year history of a recurrent rash that was pruritic, located predominantly around his waist, and associated with eosinophilia. Since this patient is from the Dominican Republic, the intermittent rash could be caused by infection with human T-lymphotropic virus type 1 (HTLV-1). This virus, which is endemic in the Caribbean and the Dominican Republic,[19] causes tropical spastic paraparesis and adult T-cell leukemia. It also causes an infective dermatitis syndrome that is characterized by an eczematous rash in a seborrheic distribution and is associated with recurrent streptococcal or staphylococcal skin and mucosal infections.[20] The rash associated with HTLV-1 usually emerges in childhood and is not consistent with the rash described in this case.

Figure 1 (facing page). Life Cycle of *Strongyloides stercoralis*.

Strong. stercoralis can complete its life cycle in the external environment (free-living cycle) or inside a human host (parasitic cycle). Rhabditiform larvae develop into either adult nematodes or filariform larvae, the infectious form of *Strong. stercoralis*, which can penetrate human skin, often through the foot. Filariform larvae then gain access to the venous or lymphatic system and migrate to the lungs, from where they break through alveoli, move up the bronchial tree, and are swallowed. Adult nematodes lodge in the epithelium of the small intestine and lay eggs that hatch into rhabditiform larvae, the majority of which leave the host through the stool. Some of these rhabditiform larvae develop into filariform larvae in the intestine; this is a key characteristic of strongyloides biology that permits autoinfection, which is initiated when these filariform larvae penetrate the perianal skin or the intestinal mucosa. In the strongyloides hyperinfection syndrome, a large number of filariform larvae complete the parasitic cycle. Data are from the Centers for Disease Control and Prevention (www.cdc.gov/parasites/strongyloides/biology.html).

This patient's recurrent rash was associated with intermittent eosinophilia. Infection with a hookworm can cause cutaneous larva migrans (a migratory, pruritic dermatitis) and peripheral eosinophilia. A number of other parasitic infections, such as gnathostomiasis, onchocerciasis, loiasis, fascioliasis, and paragonimiasis, can cause skin lesions and eosinophilia, but the patient has not had exposure to the pathogens that cause these diseases. Another notable feature of the patient's pruritic skin lesions is that they occurred predominantly around the waist and thighs. Infestation with scabies or pubic lice can cause an intensely itchy rash in this distribution, and scabies can result in a generalized urticaria.[21] In addition, the pruritic seabather's eruption is caused by sea anemone larvae that become trapped under a bathing suit and cause skin lesions; the rash of avian schistosomiasis (also known as swimmer's itch) has a similar appearance but does not occur on skin covered by clothing. However, these rashes are not transient and do not recur in the manner described in this patient.

One possible explanation that can account for



this patient's pruritic rash and intermittent eosinophilia is chronic strongyloidiasis. The intestinal nematode *Strongyloides stercoralis* is endemic in tropical and subtropical areas, such as the Dominican Republic, and can survive for decades in a single host because it can complete its life cycle inside the human body without passing into the environment (Fig. 1).[22] Patients with

chronic strongyloidiasis often have fluctuating eosinophilia,[23] intermittent abdominal pain, and recurrent rashes,[24] the two most common of which are urticaria around the waist and buttocks and larva currens, a rapidly migrating serpiginous dermatitis.[25] These symptoms develop as filariform larvae, the infectious form of *Strong. stercoralis*, initiate the autoinfection cycle by penetrating the perianal skin or the intestinal mucosa (Fig. 1).

Nine days before the current admission, the patient had received a diagnosis of contact dermatitis due to nickel allergy, which seems quite plausible given the presence of characteristic lesions on his midabdomen and anterior thighs. He was treated with prednisone for the rash, and I suspect that this was the turning point in the case.[24] Could the administration of glucocorticoids and the subsequent immunosuppression have led to the strongyloides hyperinfection syndrome?

STRONGYLOIDES HYPERINFECTION SYNDROME

The strongyloides hyperinfection syndrome can develop in patients with chronic strongyloidiasis when host immune function is impaired. The strongyloides autoinfection cycle accelerates, which leads to more egg-laying adult nematodes in the intestine and a subsequent vast increase in the number of migrating larvae (Fig. 1).[26,27] The administration of glucocorticoids[28-30] and, increasingly, the use of tumor-necrosis-factor inhibitors[31,32] are major risk factors for the strongyloides hyperinfection syndrome (also called severe complicated strongyloidiasis[23]); even short courses of these medications can cause overwhelming infection and death.[33] Eosinophilia is usually absent during hyperinfection, as it was in this case. In the most fulminant form of the strongyloides hyperinfection syndrome, called disseminated strongyloidiasis, filariform larvae can migrate to the liver, brain, kidneys, meninges, and skin. Furthermore, migrating filariform larvae can carry enteric bacteria into the bloodstream and also cause breaks in the intestinal mucosa that may provide a portal of exit for intestinal bacteria. As a consequence, bacterial sepsis, pneumonia, and meningitis are common complications of the strongyloides hyperinfection syndrome.

Bacterial meningitis that occurs concurrently with the strongyloides hyperinfection syndrome is often caused by enteric gram-negative organisms. Are any of the gram-positive cocci that can cause acute bacterial meningitis plausible pathogens in this case? Both enterococcus species and *Strep. bovis* live in the intestine and have been described as causes of meningitis in patients with the strongyloides hyperinfection syndrome.[34,35] *Strep. bovis* was formerly considered a member of the enterococcus genus, and thus it is not possible to differentiate these organisms on the basis of Gram's staining alone.

The diagnosis of the strongyloides hyperinfection syndrome can be made by examining the stool for filariform or rhabditiform larvae. This approach is not sensitive for the diagnosis of chronic strongyloidiasis, but during hyperinfection, a large number of larvae are present in the intestine, which improves the diagnostic yield of a stool sample.[25] This patient should also be tested for HTLV-1 infection, which is a risk factor for the strongyloides hyperinfection syndrome and is associated with treatment failure.[36,37]

In summary, I believe that this patient has the *Strong. stercoralis* hyperinfection syndrome with concurrent bacterial meningitis due to enteric gram-positive cocci, probably either *Strep. bovis* or enterococcus species. This case underscores the importance of testing or empirically treating for strongyloidiasis before administering immunosuppressive therapies in patients who are from or have visited areas where this infection is endemic.

Dr. Eric S. Rosenberg (Pathology): Dr. Bebell, what was your impression when you first evaluated this patient?

Dr. Lisa M. Bebell (Infectious Diseases): When we evaluated this patient, it was obvious that he had bacterial meningitis. After reviewing the Gram's staining of the CSF, we thought that the organism was morphologically consistent with enterococcus species, although we were concerned about *Strep. pneumoniae*, the most common cause of bacterial meningitis in adults. The transient and recurrent rashes, combined with the eosinophilia and the fact that he was from the Dominican Republic, led us to consider the diagnosis of chronic strongyloides infection. Alternatively, we thought the eosinophilia could be due to an allergic rash.

When we considered all the features of the patient's presentation together, we were most concerned about the strongyloides hyperinfection syndrome, particularly after his recent glucocorticoid use. Therefore, we suspected the bacteria in the CSF to be an enteric pathogen that had developed as a complication of the strongyloides hyperinfection syndrome.

We recommended serologic testing for HTLV-1 and strongyloides infection and a stool examination for ova and parasites. We treated the patient empirically for bacterial meningitis with vancomycin and ceftriaxone, to cover ceftriaxone-resistant pneumococci. We administered rifampin to facilitate the penetration of vancomycin into the CSF. Initially, we recommended empirically continuing dexamethasone to treat pneumococcal meningitis, and we also treated the patient for strongyloidiasis with ivermectin.

CLINICAL DIAGNOSIS

Strongyloides stercoralis hyperinfection syndrome, complicated by bacterial meningitis.

DR. READ PUKKILA-WORLEY'S DIAGNOSIS

Strongyloides stercoralis hyperinfection syndrome, complicated by bacterial meningitis due to enteric gram-positive cocci, probably either *Streptococcus bovis* or enterococcus species.

PATHOLOGICAL DISCUSSION

Dr. John A. Branda: Two diagnostic procedures were performed in this case. The first was lumbar puncture for the collection of CSF, which appeared cloudy on receipt in the clinical microbiology laboratory. A smear of the CSF was prepared and concentrated by cytocentrifugation, and Gram's staining was performed. Microscopic examination revealed abundant polymorphonuclear leukocytes and very few gram-positive cocci in pairs. A routine culture of the CSF revealed *Strep. gallolyticus* subspecies *pasteurianus* (formerly known as *Strep. bovis* biotype II/2), establishing the diagnosis of *Strep. bovis*–associated meningitis. In vitro testing revealed susceptibility to penicillin G and ceftriaxone.

The second diagnostic procedure, performed 3 days after admission to this hospital, was collection of a stool sample for examination for ova and parasites. The examination revealed a moderate amount of *Strong. stercoralis* rhabditiform larvae (Fig. 2), confirming the anatomical diagnosis of strongyloides infection. Moderate amounts of *Blastocystis hominis* and nonpathogenic protozoa were also identified in the stool sample.

Presumably, penetration of the intestinal mucosa during the life cycle of the helminths resulted in translocation of commensal flora, including *Strep. bovis*, into the bloodstream, leading to bacteremia and ultimately to bacterial meningitis. Thus, the final diagnosis is *Strep. bovis*–associated meningitis related to *Strong. stercoralis* infection.

Figure 2. Fecal Smear.

A *Strong. stercoralis* rhabditiform larva is seen in an unstained fecal smear. Rhabditiform (first-stage) larvae are approximately 180 to 380 μm in length by 14 to 20 μm in width, and they have a short pointed tail, a bulbous esophagus, a conspicuous genital primordium, and a short buccal canal (which is not well visualized in this image).[38]

Dr. Valentina Nardi: After the organism in the CSF was identified as *Strep. bovis*, a colonoscopy was performed to evaluate the patient for a malignant tumor. A biopsy specimen was obtained from a cecal polyp, and examination revealed polypoid colonic mucosa with expansion of the lamina propria by an exuberant inflammatory infiltrate composed of histiocytes, lymphocytes, and abundant eosinophils (Fig. 3A). Amid the inflammatory cells, two profiles of nematode larvae were seen (Fig. 3B, 3C, and 3D); the size and location of these larvae were consistent with *Strong. stercoralis*.

Interestingly, the patient had undergone a resection of a Meckel's diverticulum for a partial small-bowel obstruction 4 years before this presentation; an examination of the specimen that was performed at the time revealed no diagnostic abnormalities except for serosal fibrosis. After the diagnosis of strongyloides infection was made, we reexamined the specimen. In light of the current diagnosis, we identified a few parasites in crypts in one tissue fragment that were consistent with *Strong. stercoralis* (Fig. 4A through 4D).

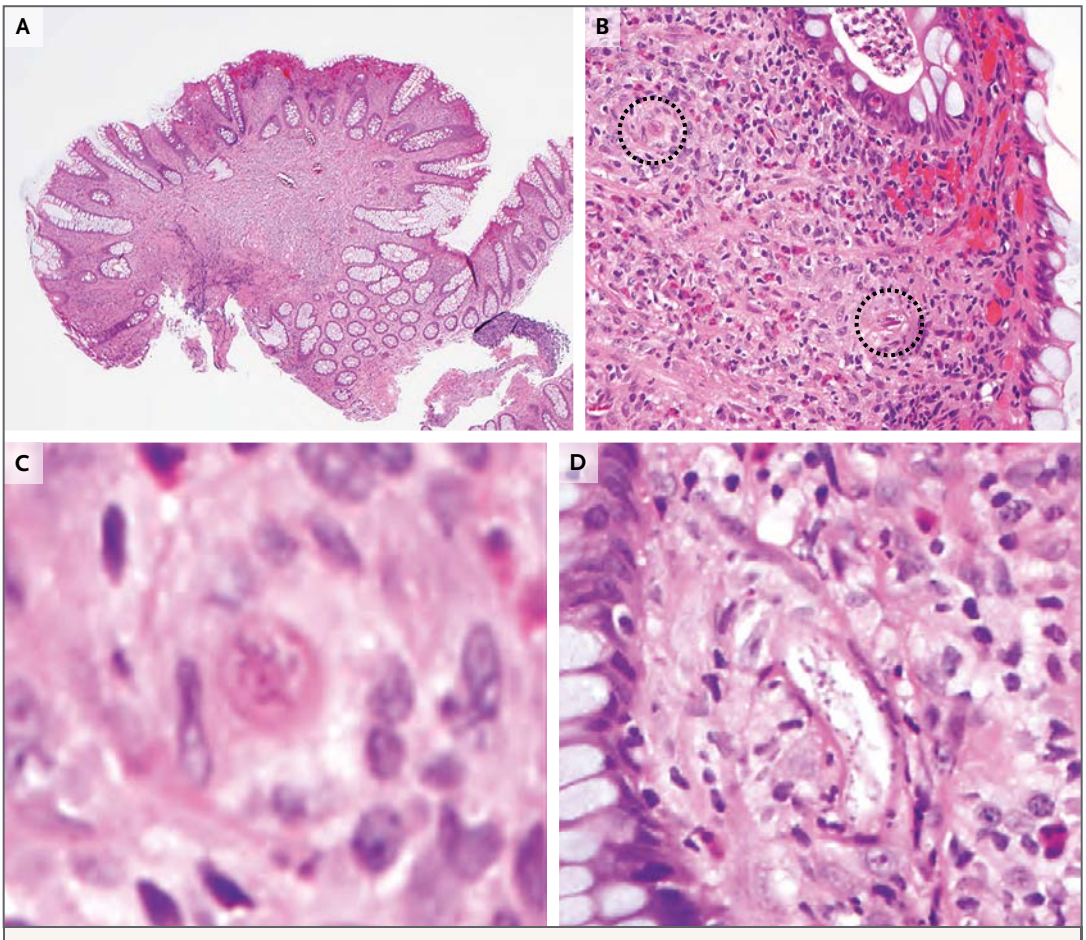


Figure 3. Biopsy Specimen from a Cecal Polyp (Hematoxylin and Eosin).

Panel A shows polypoid colonic mucosa with expansion of the lamina propria by an inflammatory infiltrate composed of histiocytes, lymphocytes, and eosinophils. Panel B shows two profiles of nematode larvae (circles). At higher magnification, Panel C shows a cross section of the larvae and Panel D shows a longitudinal section of the larvae.

FOLLOW-UP

Dr. Bebell: When a diagnosis of *Strep. bovis*–associated meningitis was made, vancomycin, dexamethasone, and rifampin were discontinued, and the patient was treated with ceftriaxone. A new cardiac murmur was found while he was in the hospital. A transthoracic echocardiogram appeared normal, but a transesophageal echocardiogram showed a 2-mm mitral-valve vegetation that was consistent with endocarditis. We changed his antibiotic therapy to penicillin and gentamicin, which he received for 4 weeks and 2 weeks, respectively. While he was in the hospital, he was treated with six doses of ivermectin for strongyloidiasis.

I saw the patient at follow-up visits 2 weeks and 5 weeks after discharge. Two weeks after discharge, he had completed gentamicin therapy without any complications. His headaches had much improved, and he had returned to work. He had no neurologic deficits but had ongoing skin discoloration in a belt-buckle distribution, presumed to be from contact dermatitis due to nickel allergy. At 2 weeks and 5 weeks after discharge, stool examinations for ova and parasites were negative for parasites. Because stool testing for strongyloides is not perfectly sensitive, we treated the patient with two additional doses of ivermectin to be certain the parasite was eliminated. A test for HTLV-1 was negative, and we concluded that his only risk factor for the strongyloides hyperinfection syndrome was glucocorticoid administration. Fortunately, the patient recovered completely from this severe illness.

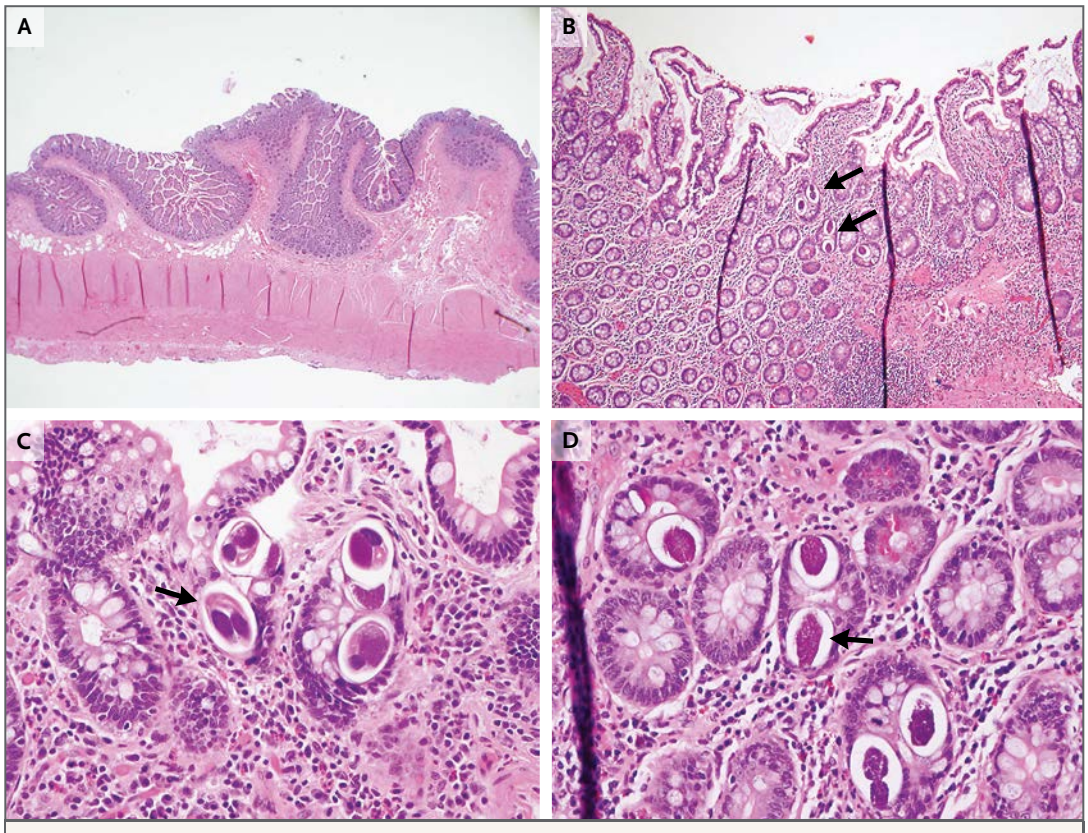


Figure 4. Biopsy Specimen from a Meckel's Diverticulum (Hematoxylin and Eosin).

A specimen from a Meckel's diverticulum resected 4 years earlier was reviewed for the presence of strongyloides larvae. The current examination of a segment of small intestine (Panel A) revealed very few ova and developing and late-stage *Strong. stercoralis* larvae (Panels B, C, and D, arrows).

DISCUSSION

Dr. Rosenberg: Was *Strep. bovis* ever detected in the patient's blood?

Dr. Bebell: Six sets of blood cultures were negative for *Strep. bovis*, but we presume that the patient had *Strep. bovis* bacteremia that caused endocarditis, as well as seeding of the central nervous system.

A Physician: The patient received dexamethasone during the initial management of the bacterial meningitis. What is the role of dexamethasone in the treatment of bacterial meningitis that occurs concurrently with the strongyloides hyperinfection syndrome?

Dr. Pukkila-Worley: In adults, adjunctive dexamethasone therapy is currently indicated for the treatment of pneumococcal meningitis.[39] Because glucocorticoids play a role in precipitating the strongyloides hyperinfection syndrome and because there is no clear indication for this therapy in the management of *Strep. bovis*–associated meningitis, it would be reasonable to discontinue dexamethasone in this patient.

A Physician: Should the patient's family members be tested for chronic strongyloidiasis?

Dr. Pukkila-Worley: If the patient's family members have the same epidemiologic risk factors for chronic strongyloidiasis as the patient does, it would be reasonable to test them for this infection. Presumed person-to-person transmission of strongyloides has been reported, but it is rare and occurs predominantly among residents in an institutional setting[40] or of long-term care facilities.[41]

FINAL DIAGNOSIS

Streptococcus bovis–associated meningitis and the *Strongyloides stercoralis* hyperinfection syndrome.

No potential conflict of interest relevant to this article was reported.

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

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