A 52-year-old Woman with Encephalopathy, Fever, and Jaundice: A Case of Disseminated Strongyloidiasis

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Presentation of Case

This is a case of a 52-year-old female admitted in the medicine ward of the Philippine General Hospital (PGH) for drowsiness, fever and jaundice. This paper will illustrate an unusual case of encephalopathy, chronic abdominal pain and jaundice due to disseminated strongyloidiasis.

Four months prior to admission (PTA), the patient sought consult for on and off right lower quadrant abdominal pain, easy fatigability, generalized body weakness, and vomiting of previously ingested food. Physical examination revealed pallor, right costovertebral angle and right lower quadrant abdominal tenderness. Work-up done showed a urinary tract infection and hookworm. An ultrasound of the kidneys and urinary bladder did not reveal any renal abscess and showed only a hyperechoic mass confirmed to be angiomyolipoma by abdominal CT scan. Bilateral renal cysts were also noted. Treatment for the urinary tract infection and hookworm were prescribed. She was lost to follow up.

One month PTA, she was admitted for one week for the persistence of the right lower quadrant pain and was managed as a case of urosepsis. She was able to regain previous functional capacity but still complained of generalized body weakness, intermittent abdominal pain and low grade fever.

One week PTA, she experienced high grade fever with steady, nonradiating right upper quadrant pain accompanied by generalized body weakness, anorexia and alteration in sensorium. Progressive decrease in sensorium prompted consult and subsequent admission.

She had a history of dry cough but no history of seizure, diarrhea, constipation, vomiting, melena, chest pain, dysuria, urinary frequency, or difficulty of breathing. Travel history revealed a 1 week stay in Bataan 5 months prior to admission. She had no other medical conditions, no previous surgeries and blood transfusions. Family history was unremarkable. She had no vices and had five pregnancies which were all delivered spontaneously at term. Menopause was at 50 years old.

She was received in the emergency department hypotensive with a palpatory blood pressure of 90. BP stabilized to 90/60 after hydration. She was tachycardic at 124 beats per minute, tachypneic at 24, febrile, disoriented and drowsy. She had pale conjunctiva and icteric sclerae. She had no cervical lymphadenopathy and JVP was normal. Auscultation revealed wheezes in the left lower lung field, heart sounds were distinct and no murmurs were appreciated. She had fluid wave but no spider angiomata. The abdominal examination was notable for diffuse abdominal tenderness most marked on the right upper quadrant. She had grade 1 bipedal edema. Neurological examination revealed nuchal rigidity, bilateral Babinski and a positive Brudzinski sign. The rest of the neurological examination was unremarkable. The assessment then was:

a. Encephalopathy likely septic-metabolic due to spontaneous bacterial peritonitis (SBP), Rule out (R/O) acute cholangitis, hepatic encephalopathy, hyponatremia, R/O Central Nervous System (CNS) infection
b. Anemia secondary to gastrointestinal loss and intestinal parasitism
c. Angiomyolipoma, right kidney

Her initial complete blood count (Table 1) showed normocytic anemia (hemoglobin 87mg/dl) and leukocytosis (13,750) with left shift (83% neutrophils). She was hyponatremic (126 mg/L), hypokalemic (2.7mg/L) and hypoalbuminemic (12mg/L). Her electrocardiogram showed diffuse T wave inversion consistent with hypokalemia. Her bleeding parameters were also deranged (2x elevated PTT and INR of 1.55). She also had direct hyperbilirubinemia but liver enzymes were normal. Urinalysis and chest x-ray were normal. Blood and urine culture had no growth after 5 days of incubation.

Ceftriaxone and metronidazole were given for suspected bacterial peritonitis. This was later shifted to piperacillin-tazobactam at 2.25 g IV every 6 hours. An abdominal CT scan revealed a generalized bowel edema but no evidence of an intraabdominal abscess, cholecystitis nor cholangitis. A lumbar tap spinal fluid analysis was not consistent with a CNS infection. The diagnostic paracentesis

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Table 1. Laboratory results

CBC		CHEMISTRY			
Hgb	87 g/dL	RBS	69.3 mg/dL	ALT	66 U/L
Hct	0.28	BUN	3.83 mmol/L	AST	132 ↑ U/L
WBC	13.75/cu mm	Crea	72 mmol/L	Amylase	65 U/L
PMN	0.83	Alb	12 ↓g/dL	Total protein	43 ↓ g/L
Lymph	0.12	Ca	2.23 mmol/L	Globulin	12 ↓ g/L
Eo	0.005	Na	126 ↓ mmol/L	PTT	
Plt	168	K	2.7 ↓ mmol/L	Cx 36.3 sec	Px 63.2 sec
MCV	N	Cl	88 mmol/L	PT	
MCH	N	TB	52.27 ↑ mg/dL	Activity	51%
Retic index	3.9	DB	45.76 ↑ mg/dL	INR	1.55
PBS	Toxic granules, slight poikilocytosis and anisocytosis	IB	6.51 mg/dL		
Malarial smear	Negative				

Urinalysis	
Color/appearance	Yellow, turbid
SG 1.020	pH 6
Sugar	Negative
Albumin	1+
RBC	0-1/hpf
WBC	1-5/hpf
Casts/crystals	Negative
Bacteria	4+
Mucus thread	Negative

Blood CS	No growth after 5 days	**Hepatitis B**	HBSAg, anti-HBS, HBeAg, anti-HBe, anti-HBc total – all nonreactive
Urine CS	No growth after 2 days	**Peritoneal fluid**	Yellow, clear, RBC 90, WBC 22, PMN 4, Lymph 18, Gluc 7.73↑, TP 3↑, PMN 0-2, Gram (+) bacilli 0-2 No growth after 5 days
CSF	Colorless, clear, RBC 0, WBC 0, gluc 6.11↑, TP 0.12↓ No growth after 5 days		

was also sterile, but it was however, performed on day 3 of IV antibiotics.

Her stool exam done twice revealed 10-20 rhabditiform *Strongyloides* larvae. Hemorrhagic gastritis was seen in esophago-gastro-duodenoscopy.

Throughout her hospital stay, she developed dyspnea with wheezing. She remained drowsy and disoriented despite correction of her hyponatremia and adequate bowel cleansing with lactulose. It was only on the 5th hospital day when her sensorium improved concurrent with lysis of her fever. She was given Albendazole 400 mg tab BID. Though she was still jaundiced and edematous, she was discharged much improved with good appetite, no abdominal pain and a normal mental status.

Discussion

Our patient presented with a four-month duration of intermittent abdominal pain and low grade fever with associated malaise and anorexia. A few weeks prior to admission, her condition worsened, this time, with high grade fever, drowsiness and jaundice.

Sepsis from spontaneous bacterial peritonitis was the primary consideration because of the high grade fever, leukocytosis, ascitis and abdominal pain. No isolate however, was obtained though the ascitic fluid analysis was done on the 3rd day of intravenous antibiotics. After isolation of the strongyloides from the stool and bronchoalveolar lavage, a disseminated form can explain all the other symptoms.

Strongyloidiasis

The S. stercoralis life cycle is composed of both free-living and parasitic stages (Figure 1). Microscopically, there are two common types of S. stercoralis larvae, rhabditoid (L1) and filariform (L3). Filariform larvae are distinguished from rhabditoid larvae by their larger size, a relatively long esophagus and a unique tail with a notched appearance.[1]

As a free-living organism, it is seen in humid soil in hot regions. When the male and female rhabditiform larvae (L1, L2) are in a favorable environment, they reproduce sexually. The females release eggs in the soil, and within a few hours, the rhabditiform larvae surface. In unfavorable soil conditions, these rhabditiform larvae transform into infective larvae, also called filariform larvae.[2]

In general, these filariform larvae cause infection when they penetrate the skin and enter the venous microcirculation via the lymphatics. What is unique about this parasite is that its sexual reproduction occurs exclusively in the free-living stage. The female S. stercoralis has the ability to complete an entire cycle of replication within the human host.[3] As it enters the lymphatics, it eventually penetrates the pulmonary alveoli, ascends into the respiratory tree, and is eventually swallowed by the host and subsequently gains access into the gastrointestinal tract.[4]

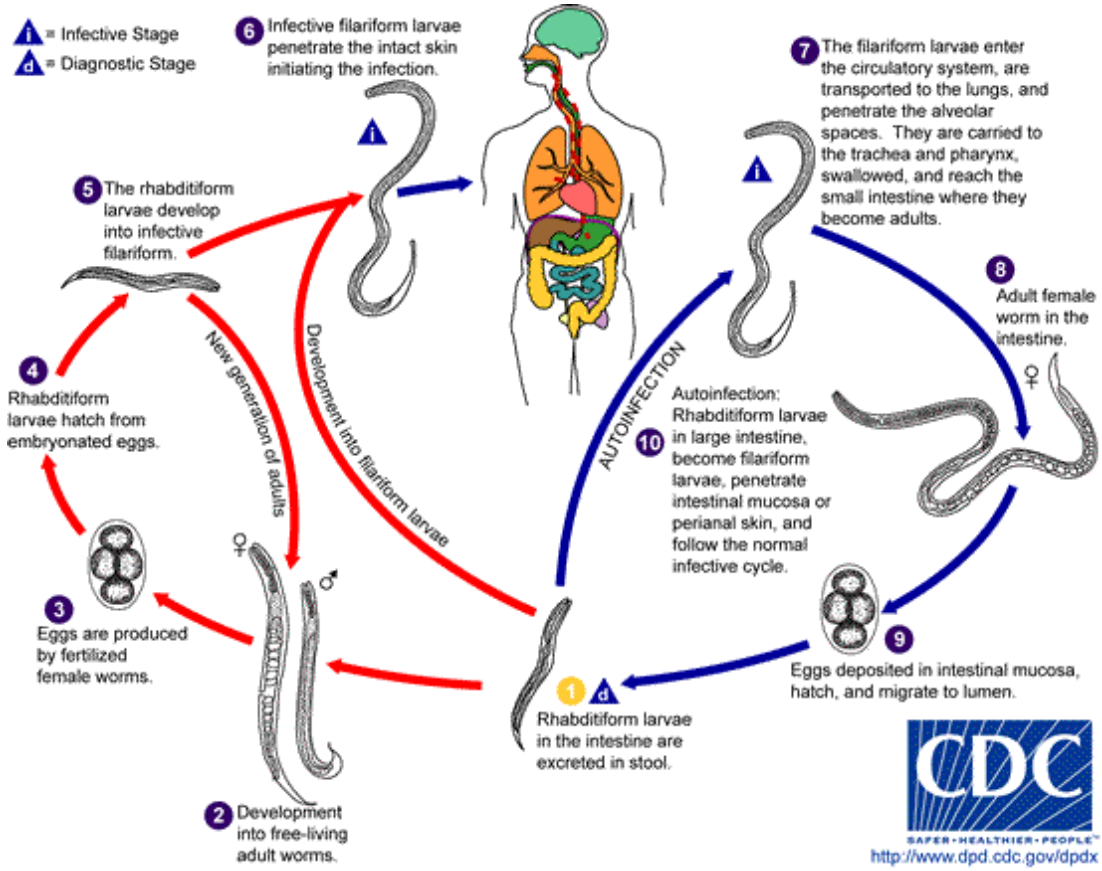

Figure 1. Life cycle of *Strongyloides stercoralis*
(Source: http://www.dpd.cdc.gov/dpdx/HTML/Strongyloidiasis.htm)[5]

It then reaches the duodenum and proximal jejunum, its preferred sites of residence where the parasitic female of S. stercoralis lives buried in the crypts of the small intestine.[1] While in the gastrointestinal tract, the larvae mature into adult worms and fertilization occurs. Adult females penetrate the mucosa of the duodenum and proximal jejunum, where they lay eggs and can remain present for years. Adult males are eventually expelled with feces.[6] These eggs hatch into rhabditiform larvae which are shed in the stool and eventually undergo the free-living stage and replicate as previously described. Some of these rhabditiform larvae may differentiate into invasive filariform larvae. In this form, they are capable of reinfecting the host by invading the intestinal wall and perianal skin and reenter the intestinal-pulmonary-intestinal phase of the life cycle.[3,7] The initial symptoms occur soon after the infective filariform larvae gain entry into the human host. A serpiginous urticarial rash known as larva currens may be seen at the site of entry and is thought to be pathognomonic for the infection.[6,8] Most common gastrointestinal symptoms are diarrhea, abdominal pain, bloatedness, and progressive weight loss.[2,4,9] Although to include strongyloidiasis in the differential diagnosis requires a high index of suspicion, once suspected, a definitive diagnosis can be made by the detection of *Strongyloides* larvae in stool or body fluids.[6,8,10] However, larvae are released only intermittently and therefore may not be appreciated with a single determination. In a majority of uncomplicated cases, the intestinal worm load is often very low and the output of larvae is minimal. It has been shown that a single stool examination fails to detect larvae in up to 70% of cases. Repeated studies improve the chances. In some studies, diagnostic sensitivity increases to 50% with three stool examinations and can approach 100% if seven serial stool samples are examined.[11] The majority of patients with *Strongyloides* infection have uncomplicated disease, with 50% remaining asymptomatic.[6] The respiratory system is the organ most commonly affected outside the gastrointestinal system with symptoms such as nonproductive cough, wheezing and dyspnea.[2,9]

Hyperinfection Syndrome

Hyperinfection syndrome refers to an increase in parasite burden due to acceleration of autoinfection cycle without an accompanying spread of larvae outside the usual migration pattern.[4] In general, but not always, this is the

result of an alteration in the immune status. Development of or exacerbation of gastrointestinal and pulmonary symptoms is seen, and the detection of increased numbers of larvae in stool and/or sputum is the hallmark of hyperinfection.[3] The clinical manifestations of hyperinfection vary and result from the enormous multiplication and migration of infective larvae.[8] Intestinal manifestation may include severe cramping, abdominal pain, watery diarrhea, weight loss, nausea, vomiting, intestinal obstruction, paralytic ileus, malabsorption, and occasionally gastrointestinal bleeding.[5,8] As in the acute state, the lung is the most common extraintestinal organ affected in the hyperinfection state.[4] Pulmonary symptoms due to migrating larvae resemble Loeffler's syndrome with asthma-like manifestations such as cough and wheezing, pneumonia, pulmonary hemorrhage, respiratory insufficiency, diffuse bilateral and lobular infiltrates, lung abscess, and acute respiratory distress syndrome.[4,6,8] Strongyloides found on both stool and BAL confirmed the diagnosis of hyperinfection.

Disseminated Strongyloidiasis

Disseminated strongyloidiasis is defined as the systemic spread of invasive filariform larvae to sites outside their normal migration pattern with extensive invasion to virtually every organ. While dissemination implies coexisting hyperinfection, hyperinfection can occur without dissemination.[4] It is important to recognize disseminated infection as this has a mortality rate of 83-87%.[4] Although the mechanism for dissemination is not very well understood, it is believed that impaired host immunity plays a role. In disseminated infection, involvement of other organ systems such as the central nervous system may occur, with symptoms including headache, altered mental state, focal seizures, and in extreme cases, coma.[4] The liver may also be affected manifesting as an obstructive pattern in liver enzymes, with elevations of the alkaline phosphatase and bilirubin, and to a lesser extent, alanine aminotransferase and aspartate aminotransferase. Other organ systems which may be involved include the skin, mesenteric lymph nodes, gallbladder, diaphragm, heart, pancreas, skeletal muscle, kidneys, and ovaries.[3] Secondary infections in the form of gram-negative or polymicrobial bacteremia may occur. Foreman et al. proposed three mechanisms for entry of these microbes into the bloodstream producing secondary infection 1) the integrity of the intestinal mucosa is disrupted, which allows the enteric bacteria to enter the bloodstream, 2) enteric pathogens enter the bloodstream attached to the *Strongyloides* larvae, 3) enteric organisms enter the bloodstream as they are excreted by the parasites already in the circulation.[6]

Treatment

Clinical trials assessing drug treatment of *S. stercoralis* infection have, for the most part, dealt with chronic infection rather than hyperinfection or dissemination. The criteria for success in these studies are improvement in symptoms and negative stool exams.[3] The goal for treatment is eradication rather than suppression or symptomatic improvement as it only takes one worm to once again resume the cycle of autoinfection. The regimens to accomplish this are not clearly defined.

The azole drugs have been used for many years. Thiabendazole has been the drug of choice for many years but has fallen out of favor due to the prominence of gastrointestinal side effects, such as liver dysfunction, nausea, anorexia, and dizziness, and a high relapse rate.[12] Mebendazole has also been used to successfully treat a number of cases of hyperinfection. It is, however, poorly absorbed, and the decreased accessibility to migrating larvae may have played a role in its therapeutic effectiveness.[3] Albendazole, the newest of the three, at 400 mg twice a day for three days has been shown to clear stool of S. stercoralis larvae in 38% to 45% of infected individuals with few side effects noted. Therapy is extended from seven to fourteen days following a well documented negative stool exam.[3,4]

Conclusion

Patients with disseminated strongyloidiasis often present as a diagnostic challenge. Not all physicians may be familiar with the disease and its manifestations leading to its non-inclusion in the differential diagnosis. The clinical manifestations are nonspecific and may lead the physician to other diagnosis. Furthermore, superinfections especially in the setting of hyperinfection and dissemination may be present. Apart from nonspecific symptoms, the symptomatology may also be varied from asymptomatic eosinophilia to a multi-organ failure.

The key to a prompt diagnosis is a high index of suspicion, especially in areas of high endemnicity. Patients who present with gastrointestinal and pulmonary complaints with unexplained gram negative bacteremia or sepsis should alert the physician to the possibility of strongyloidiasis, as in our patient who presented with chronic abdominal pain and an acute onset of dyspnea. It is important to consider this rare but treatable condition in patients presenting similarly especially in the Philippines where *Strongyloides stercoralis,* initially discovered in Northern Luzon, is considered to be endemic in rural areas in the Philippines.

Final Clinical Diagnosis: Disseminated Strongyloidiasis

Addendum:

A single stool examination will detect rhabditiform (rhabdoid) larvae 25% of the time. Multiple stool examinations utilizing concentrated stool, zinc flotation, the Baermann technique (feces-concentrating procedure), or agar-plate method increase sensitivity to 85%. Examination must be performed on fresh stool specimens not allowed to stand at room temperature for more than 3 hours because rhabdoid larvae may transform into filariform larvae and the erroneous diagnosis of hyperinfection (or dissemination).[4]

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