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STRONGYLOIDES STERCORALIS AND CANCER

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Abstract

Strongyloidiasis is caused by infection with *Strongyloides stercoralis*. Manifestations of infection can range from asymptomatic eosinophilia in immunocompetent host to disseminated disease with septic shock in the immunocompromised host. Strongyloidiasis is endemic in tropical and subtropical regions and occurs sporadically in temperate areas. Burden of adult worms in infected humans can increase substantially via autoinfection. Among immunocompromised hosts, autoinfection can lead to hyperinfection syndrome where there is massive dissemination of filariform larvae to the lungs, liver, heart, central nervous system, and endocrine glands. Most infected patients do not experience prominent symptoms. The most common manifestations are mild waxing and waning gastro-intestinal, cutaneous, or pulmonary symptoms that persist for years; others simply have eosinophilia in the absence of symptoms.

Keywords: *Strongyloides stercoralis,* Immunocompetent & Immunocompromised hosts, pathogenesis.

Introduction

Strongyloidiasis is endemic in tropical and subtropical regions and occurs sporadically in temperate areas. In tropical and subtropical regions the overall regional prevalence may exceed 25%. The highest rates of infection in the United States are among residents of the southeastern states and among individuals who have been in endemic areas as immigrants, refugees, travelers and military personnel (Posey *et al*, 2007). A Canadian study of newly arrived Southeast Asian refugees identified strongyloidiasis seroprevalence among Kampucheans, Laotians, and Vietnamese (76, 56, & 12%, respectively). In another study, over 40% of Cambodian immigrants to Australia had positive or equivocal strongyloides serology indicating possible infection (Caruana *et al*, 2006). *Strongyloides stercoralis,* an intestinal nematode, can cause strongyloidiasis and gastrointestinal ulcer. *S. stercoralis* infects about 50-100 million people in tropical and subtropical regions (Segarra-Newnham, 2007). About 50% of individuals *S. stercoralis* chronically infected are asymptomatic while symptomatic forms may lead to severe skin pathology, diarrhea, nausea, and abdominal discomfort. Infection with *S. stercoralis* may be complicated by autoinfection that resulted in a hyperinfection syndrome and was associated with sustained infection, high worm burden and high mortality (Segarra-Newnham, 2007).

Life cycle begins when human skin contacts infective filariform larvae, which are found in soil or other materials contaminated with human feces. Larvae penetrate the skin and migrate hematogenously to the lungs and penetrate into the alveolar air sacs. The larvae then ascend the tracheobronchial tree and are swallowed (Schupf *et al*, 1995). The larvae mature into adult worms that burrow into the mucosa of duodenum and jejunum. Adult worms may live for up to five years. Adult female produces eggs which hatch noninfectious larvae (rhabditiform larvae) develop within the lumen of gastrointestinal tract. Rhabditiform larvae are generally passed in the feces. The cycle from dermal penetration to appearance of larvae in the stool requires approximately 3 to 4 weeks (Lindo *et al*, 1995).

S. stercoralis can complete its life cycle entirely within the human host (autoinfection), increasing the burden of adults in infected humans substantially via the autoinfection cycle. Rhabditiform larvae mature into the filariform larvae within the gastrointestinal tract that can penetrate perianal skin or colonic mucosa to complete the autoinfection cycle. Larval transformation within

the gastrointestinal tract may also be accelerated by constipation, diverticula, other conditions that reduce bowel motility, and steroid use (Siddiqui *et al*, 2006).

Although autoinfection is limited by an intact immune response, in a low autoinfection level organism may persist for decades and cause clinical manifestations long after initial infection (Chu *et al*, 1990), in Thailand prisoners of war who were infected for more than 40 years (Pelletier *et al*, 1988). But, because of autoinfection, human strongyloidiasis can persist even for the patient lifetime (Wilson, 1991). In patients with depressed cell-mediated immunity, autoinfection caused fatal hyperinfection with disseminated disease (Keiser and Nutman, 2004). Densely urbanizing areas lead to an increase in available food for insects, and areas with poor sanitation and hygiene practices attract disease-carrying insects such as those within the order Blattodea and Diptera. Their preference for consuming wet, rotting substances indicates a high probability for the consumption and carriage of *Strongyloides* spp. was on the external body of house flies and cockroaches (Förster *et al*, 2009). *Strongyloides* spp. was found in feces of ruminants used in western farming settings including pigs, sheep, and cattle (de Souza *et al*, 2012). Also, dogs, primates, mud soil, stagnant water, fruit and vegetables contained infective larvae, capable of perpetuating infection within humans who have come into contact settings (White *et al*, 2019).

Review and Discussion

Clinical manifestations: Most patients did not experience prominent symptoms. The commonest manifestations are mild waxing and waning gastrointestinal, cutaneous, or pulmonary symptoms that persist for years; others simply have eosinophilia in the absence of symptoms. But, eosinophilia is not universally present in strongyloidiasis (Nutman *et al*, 1987). Intestinal parasitism with one or more organisms was responsible for the eosinophilia in 122; hookworm (55%) and *S. stercoralis* (38%) were the commonest organisms. However, eosinophilia may be suppressed or absent in disseminated disease because of concomitant pyogenic infection or steroid administration. The serum IgE concentration was often elevated in these settings (Robinson *et al*, 1994)

Strongyloides stercoralis may produce cutaneous reactions when larvae penetrate the skin, sometimes termed ground itch. These reactions include inflammation, edema, petechiae, serpiginous or urticarial tracts, and severe pruritus. The feet are the commonest affected site with initial infection, but dermal manifestations of primary infection rarely led patients to seek medical attention (Meinking *et al*, 2003). With chronic infection, urticaria or pruritis can develop. Also, the dermal migration of larvae may produce a distinctive eruption at other sites, most commonly on the buttocks. As larvae migrate, at a rate detectable by observers, a serpiginous, raised, erythematous track develops, and these lesions are pathognomonic of strongyloidiasis or larva currens (running larva). Other skin lesions in chronic strongyloidiasis may include in disseminated infections angioedema (Mehta *et al*, 2002), nonpalpable purpura (Reddy and Myers, 2003), erythroderma that mimics drug reaction (Ly *et al*, 2003).and periumbilical purpura (Salluh *et al*, 2005a).

Gastrointestinal symptoms: Adult worms in small bowel induce duodenitis, which can lead to upper abdominal pain. Patients may also experience diarrhea, anorexia, nausea, and vomiting. Epigastric pain may mimic duodenal ulcer, except that food ingestion may aggravate pain of strongyloidiasis. Chronic enterocolitis and malabsorption can result from a high intetinal worm burden (Scowden *et al*, 1978).

Pulmonary manifestations: The transpulmonary migration of larvae can produce dry cough, throat irritation, dyspnea, wheezing, and hemoptysis. A Loeffler's-like syndrome with eosinophilia was rarely reported. Some patients with chronic strongyloidiasis experience repeated fever episodes and mild pne-

umonitis, producing a picture that resembles recurrent bacterial pneumonia. Eosinophilia is often absent initially, but may develop later in infection. Strongyloidiasis treatment terminates the episodes of pneumonia. Chronic strongyloidiasis patients may also develop asthma that paradoxically worsens with corticosteroid use (Sen *et al*, 1995) or dyspnea due to restrictive pulmonary disease (Lin *et al*, 1995). Strongyloidiasis can be presented as acute respiratory failure or pulmonary embolism (Newberry *et al*, 2005).

Hyperinfection syndrome: Autoinfection cycle lead to hyperinfection syndrome by increasing the parasite burden greatly. Autoinfection within the gastrointestinal tract begins when rhabditiform larvae transform into filariform larvae, which penetrate the intestinal wall to enter bloodstream. Massive filariform larvae dissemination to lungs, liver, heart, CNS, and endocrine glands induces inflammation resulting in symptomatic dysfunction of these organs or even septic shock (Cebular *et al*, 2003). The commonest manifestations of the hyperinfection syndrome include: fever, nausea and vomiting, anorexia, diarrhea, abdominal pain, dyspnea, wheezing, hemoptysis and/or cough (Strazzella and Safirstein, 1989).

The chest radiograph reveals pulmonary infiltration of foci of hemorrhage, pneumonitis, and edema (Lam *et al*, 2006). Rarely, adult worms localized in the bronchial tree laid eggs and developed into larvae in airway. Bronchospasm frequently accompanied such hyperinfection manifestation (Nwokolo and Imohiosen, 1973).

Clinical features of hyperinfection syndrome may be attributable to direct consequences of organ invasion by the filariform larvae or to secondary Gram negative bacteria, pneumonia, or even meningitis due to bloodstream seeding originated from gastrointestinal tract or lungs (Ghoshal *et al*, 2002). Eosinophilia may be absent when complications such as Gram negative bacteria, mortality rates of 10 to >80% in the hyper-infection syndrome (Walker and Zunt, 2005).

Role of immunosuppression: Likelihood of hyperinfection syndrome developing increased if cell-mediated immunity was impaired by congenital immunodeficiency, underlying malignancy, malnutrition, alcoholism, hematopoietic stem cell transplantation (HSCT), or the administration of corticosteroids or cytotoxic drugs (Schaeffer *et al*, 2004). Even short corticosteroids courses (6 to 17 days) have led to overwhelming hyperinfection and death (Ghosh and Ghosh, 2007. The pathophysiology underlying these risk factors, whether disease-related or genetically induced, was a compromised immune system that led to dysfunction of TH-2 helper cells (Concha *et al*, 2005). Thus, it was indicated to detect and eradicate strongyloidiasis prior to start immunosuppressive therapy. But, due to immunosuppressive therapy consisting of chemotherapeutic drugs and/or corticosteroids, and the progressive nature of many tumors (Keiser and Nutman, 2004), cancer patients who are generally immunosuppressed are at risk of developing hyperinfection (Kia *et al*, 2008). Numerous reports have documented association of immunosuppressive therapy and steroids as a primary cause of fatal strongyloidiasis hyperinfection in cancer patients (Abdelrahman *et al*, 2012; Norsarwany *et al*, 2012).

In comparison with steroids and cytotoxic agents, cyclosporine has activity against strongyloidiasis (Schad, 1986). It is unknown, however, whether this effect is sufficient to reduce the risk of hyperinfection in patients receiving cyclosporine.

Notably, hyperinfection with *S. stercoralis* was reported to be in part geographically associated with the occurrence of HTLV-1 infections. An epidemiological study investigated the association of co-infection with *S. stercoralis* and HTLV-1 with cancers in a large cohort of 5209 cancer patients and showed that *S. stercoralis* infection was caused an increased occurrence of cancers (Tanaka *et al*, 2016). HTLV-1 caused adult T cell leukaemia/lymphoma by enhanced the immortalization and transformation of T ce-

lls and thus was classified as a Group 1 carcinogen (IARC, 2012). The HTLV-1 proteins Tax and HBz are involved in many regulatory processes including the induction of growth of infected T cells, transformation, transcription of cellular genes, and genetic instability. HTLV-1 proviral loads were significantly higher in HTLV-1 carriers with strongyloidiasis than in HTLV-1 positive individuals without *S. stercoralis* infection suggesting that *S. stercoralis* may stimulate HTLV-1 replication (Gabet *et al,* 2000). Generally, the helminth infection induced polyclonal expansion of HTLV-1-infected T cells by activation of IL-2/IL-2R system (Satoh *et al,* 2002), suggesting that *S. stercoralis* is a cofactor for development of HTLV-1-induced lymphoid cancers.

Previously, Genta (1989) reported that *S. stercoralis* colitis proved to be a severe but, an easily curable disease with a high mortality rate if left untreated. He added that strongyloidiasis could persist up to several decades and might lead to a chronic colitis similar to that seen in inflammatory bowel disease, with confusion between both. Xie and Itzkowitz (2008) in USA stated that patients with long-standing inflammatory bowel disease (IBD) have an increased risk of developing colorectal cancer (CRC), as many of the molecular alterations were responsible for sporadic colorectal cancer, namely chromosomal instability, microsatellite instability, and hypermethylation. They added that this have a role in colitis-associated colon carcinogenesis and colon cancer risk in inflammatory bowel disease increases with longer duration of colitis, greater anatomic extent of colitis, the presence of primary sclerosing cholangitis, family history of CRC and degree of inflammation of the bowel. Besides, Seo *et al*. (2015) reported that a Korean patient had both *S. stercoralis* infection and early gastric adenocarcinoma. Further analysis showed that the gastric adenocarcinoma and adenoma tissues were positive for *S. stercoralis* suggesting a causative effect of *S. stercoralis*. An association of colorectal cancer with chronic strongyloidiasis was also reported in a Columbian patient (Tomaino *et al,* 2015). These reports suggest that *S. stercoralis* may not only serve as a cofactor for induction of HTLV-1-related lymphoid cancers, but also stimulates induction of colon adenocarcinoma probably by interacting with the host and /or activating host immune response. Althumairi *et al.* (2016) in USA stated that inflammatory bowel disease (IBD) was associated with increased risk of colorectal cancer (CRC), they added that colorectal cancer, as IBD-associated neoplasia required a restorative proctocolectomy with ileal pouch-anal anastomosis. Catalano *et al*. (2017) reported a 47-year-old Colombian man with a history of vitiligo and chronic anemia was admitted with chronic, intermittent abdominal pain, fatigue, and an unintentional 25-pound weight loss over 6 months, without personal or family history of colon polyps, colorectal cancer, celiac disease, or inflammatory bowel disease. The case was diagnosed as chronic strongyloidiasis colitis associated with colorectal cancer.

Underlying HTLV-1 infection was a significant risk factor for disseminated disease with strongyloidiasis (Rahim *et al,* 2005). Patients with HTLV-1 infection have high levels of interferon-gamma production that decreased production of IL-4, IL-5, IL-13, & IgE, important molecules in the host defense against strongyloidiasis (Carvalho and Da Fonseca-Porto, 2004). Regulatory T cells play a role in susceptibility to strongyloidiasis hyperinfection; among patients with HTLV-1 and strongyloidiasis co-infection, regulatory T cell counts are increased and correlated with both low circulating eosinophil counts and reduced antigen-driven IL-5 production (Montes *et al,* 2009)

Disseminated strongyloidiasis can occur in AIDS patients (Celedon *et al,* 1994), but with less frequently than in HTLV-1 patients and was much less common than might be predicted given the co-endemicity of the two infections. However, immune reconstitution was a risk factor for disseminated strongly-

oidiasis (Taylor *et al,* 2007), or malignant malaria (Saleh *et al,* 2019) and HIV positive patients may be at risk for strongyloidiasis treatment failure (Viney *et al,* 2004).

Other conditions or medications may be associated with an increased risk of strongyloidiasis: 1- Hypogammaglobulinemia (Seet *et al*, 2005), 2- Anti-TNF receptor therapy (Krishnamurthy *et al,* 2007). 3- Immunosuppression associated with organ transplantation (Marty, 2009).

Testing for strongyloidiasis is indicated for individuals in the following categories: 1- Patients with clinical manifestations and epidemiologic exposure as described (unexplained eosinophilia, urticarial or serpiginous skin lesions, or pulmonary or gastrointestinal symptoms). 2- Immunosuppressed patients (steroid & other immunosuppressive treatments, HTLV-1 infection, hematologic malignancy, malnutrition, AIDS) without explained eosinophilia, history of characteristic skin lesions, or epidemiologic exposure (Nuesch e*t al,* 2005). Transplant candidates should also be tested prior to immunosuppression if they have a potential exposure history (Roxby *et al*, 2009). 3- Asymptomatic individuals such as immigrants, refugees, long term travelers, or military personnel who have been in a known endemic for strongyloidiasis areas, even if their last exposure was decades prior (Johnston *et al,* 2005). 4- In endemic regions, patients with invasive infections caused by enteric organisms (mainly systemic Gram negative bacterial infections) without an obvious cause (Agrawal *et al*, 2009)

Diagnosis: Diagnosis of uncomplicated strongyloidiasis is usually done by detecting rhabditiform larvae in concentrated stool or via serologic methods, larvae first appear in the stool three to four weeks after initial dermal penetration (Beal *et al*, 1970).

Detection of larvae: Standard stool examination was notoriously insensitive for detecting *Strongyloides* 50% sensitivity (Boulware *et al,* 2008). This was due to larvae excretion only intermittently, and many patients have a low burden of infectious parasites. Specialized tests on stool samples included the Baerman concentration technique, the Harada-Mori filter paper technique, and a modified agar plate method can increase the yield, but even three or more stool examinations can fail to detect *Strongyloides* (Hirata *et al,* 2007). Of the specialized techniques, the agar plate method is commonly used and is most sensitive (Ramanathan and Nutman, 2008). It involves inoculating agar plates with stool and incubating for two days at room temperature. Larvae crawl on the agar and spread bacteria in their paths, creating bacterial growth patterns on the agar surface. Larvae can be seen by macroscopic examination of the plates and their presence confirmed with formalin washing of the plate surface and examination of the sediment from the washing (Greiner *et al,* 2008).

Aspiration of duodenojejunal fluid or the use of a string test (Enterotest), sometimes detects *Strongyloides* larvae in patients with negative stool samples. Alternatively, serologic testing may be helpful (Smith *et al,* 1985). In disseminated strongyloidiasis, filariform larvae can be found in stool, sputum, bronchoalveolar lavage fluid, pleural fluid, peritoneal fluid, and surgical drainage fluid (Eveland *et al,* 1975). Sputum should also be examined for larvae if disseminated strongyloidiasis is suspected (Abdalla *et al,* 2005). For patients with rash, larvae may be visualized by skin biopsy.

PCR tests have also been developed for detection of *Strongyloides* in stool samples, but are not widely available. In one study, stool samples analyzed by microscopic examination were positive for *Strongyloides* in 0.1%, compared with 0.8% positivity when the same samples were tested via PCR (ten Hove *et al,* 2009).

Serology: Diagnosis of strongyloidiasis by ELISA has proven useful in immunocompetent individuals, both in symptomatic and asymptomatic strongyloidiasis. ELISA may be positive even if repeated examinations of stool samples are unrevealing (Carroll *et al,* 1981). In *S. stercoralis* infection ELISA det-

ects the filariform larvae' IgG. Negative test results in immunocompetent subjects decrease the likelihood that infection is present; however, some ELISA serologies done by commercial laboratories gave variable reliability (Savage *et al*, 1994), and to monitor long term treatment efficiency by detecting changes in parasite-specific antibody isotypes (Satoh *et al*, 1999). But, ELISA results can be false negative in immunocompromissed hosts, mainly in presence of other helminthiasis (Neva *et al*, 1981). The two commercially available ELISAs (IVD-ELISA & Bordier-ELISA) were found to have sensitivity of 89 & 83%, respectively, and 97.2% specificity for both in diagnosing intestinal strongyloidiasis (van Doorn *et al*, 2007)

Indirect immunofluorescence assays have also been developed, as has a gelatin particle agglutination test (Boscolo *et al*, 2007). A newer technique, luciferase immunoprecipitation system (LIPS), is another attractive alternative to ELISA-based methods (Ramanathan *et al*, 2008)

Endoscopy: Upper endoscopy is not always needed for stronglyoidiasis diagnosis. However, it may be performed in patients with gastrointestinal symptoms with unsuspected disease. Strongyloidiasis has a wide range of endoscopic features (Sreenivas *et al*, 1997): In duodenum, there are edema, brown discoloration of mucosa, erythematous spots, subepithelial hemorrhages, and megaduodenum. In colon, there are loss of vascular pattern, edema, aphthous ulcers, erosions, serpiginous ulcerations, and xanthoma-like lesions. In stomach, there are thickened folds and mucosal erosions (Thompson *et al*, 2004).

Larvae may be demonstrated on biopsies of the affected mucosa (Overstreet *et al*, 2003).

Strongyloides colitis can sometimes mimic ulcerative colitis, but distinctive features of the strongyloidiasis include: skip pattern of the inflammation, distal attenuation of the disease, eosinophil-rich infiltrates, relatively intact crypt architecture, and frequent involvement of submucosa (Qu *et al*, 2009).

Differential diagnosis: The differential diagnosis for strongyloidiasis (nonspecific gastrointestinal and/or pulmonary symptoms, or chronic urticaria and/or pruritus) is broad. In larva currens patients the most important alternative diagnosis is cutaneous larva migrans, or urticarial rash along buttocks, perineum, and thighs due to repeated auto-infection described as rapidly as 10cm/hr.

Treatment: Uncomplicated infection: In the past, thiabendazole was administered for uncomplicated infection. However, thiabendazole is now rarely used due to the availability of more efficacious and better tolerated medications. Treatment of choice for strongyloidiasis is *ivermectin* with *albendazole* as an alternative. *Ivermectin* is usually given as two single 200mcg/kg doses either on two consecutive days or two weeks apart. If oral and/or rectal administrations are not possible, there have been instances where investigational new drug (IND) exemptions for the veterinary subcutaneous formulation of the ivermectin have been granted by the FDA. Relative contraindications include: 1- Confirmed or suspected concomitant *Loa loa* infection. 2- Patients weighing less than 15kg, and 3- Pregnant or lactating women

Among 88 strongyloidiasis patients 31 received thiabendazole 25mg/kg/12hours for 3 consecutive days; 22 received ivermectin 200mcg/kg as a single dose, and 35 received ivermectin for 2 consecutive days. Efficacy rates were 78, 77, & 100% in thiabendazole, ivermectin single-dose, and ivermectin two-dose regimens, respectively. Patients (16%) taken thiabendazole experienced side effects compared to 3% in combined ivermectin ones (Igual-Adell *et al*, 2004). African immigrants from loiasis endemic areas, they must be screened to exclude microfilaremia high levels, due to ivermectin administration to highly microfilaremic patients may precipitate the life-threatening encephalopathy (El-Bahnasawy *et al*, 2016).

Massoud *et al.* (2006) successfully treated 25/28 Egyptian strobgyloidiasis cases by mirazid® (100mg daily for 5 days repeated at 2 weeks intervals) for one month. Only one

of the 3 resistant cases 1 responded to repeated mirazid course, and 2 responded to combined therapy of mirazid and mebendazole.

Albendazole: Albendazole (400mg PO twice daily for 3 to 7 days) proved active against strongyloidiasis (Muennig *et al*, 2004). Efficacy of albendazole was lower than that of ivermectin, with a mean of 60% effectiveness for 3 days of albendazole versus 92% for ivermectin. Among 42 Thai chronic strongyloidiasis patients was 90% cure rate by a single dose of ivermectin compared to 50% for 7 days of albendazole 800mg/day (Suputtamongkol *et al*, 2008).

Disseminated disease/hyperinfection syndrome: The optimal treatment of disseminated disease and hyperinfection is uncertain, as data are limited. In immunocompromised patients with disseminated disease, reduction of immunosuppressive therapy, if possible, is an important adjunct to any anthelminthic therapy. In such cases it was also usually necessary to prolong or repeat ivermectin therapy, although there was no generally agreed upon regimen. Some experts gave 5 to 7 days of ivermectin in disseminated disease, or combined ivermectin with albendazole until the patient responds. Often treatment duration was determined by patient's response; daily ivermectin should be administered until symptoms resolve and stool tests were negative for at least 2 weeks (an auto-infection cycle), or longer if immunosuppressed patient (Segarra-Newnham, 2007).

The optimal treatment of critically ill patients with the hyperinfection syndrome is uncertain; data regarding ideal dose, duration, and route of therapy is limited. In hyperinfection strongyloidiasis patients unable to receive oral therapy due to ileus or obtundation, alternative (not FDA-approved) regimens included subcutaneous ivermectin as 200mcg/kg (Leung *et al*, 2008), per rectal ivermectin administration (Tarr *et al*, 2003), and a parenteral veterinary formulation of ivermectin were used with variable success (Miller *et al*, 2008). Combined longer term ivermectin and albendazole proved successful in a case of refractory strongyloidiasis. Ongoing monthly doses of ivermectin for at least six months may be given in the setting of ongoing immunosuppression among survivors of hyperinfection syndrome (Pornsuri yasak *et al*, 2004).

Patient monitoring: Patients on strongyloidiasis treatment should have follow-up stool examinations, complete CBC with eosinophilia and serology (Salluh *et al*, 2005b).

Treatment failures may occur even with ivermectin in non-immunocompromised hosts. If stool examinations were positive for larvae prior to treatment, repeat stool examinations should be performed about 2 to 4 weeks after treatment. However, a negative stool examination was not definitive proof of parasitologic cure since stool examsinations are insensitive for larval detection. Persistent symptoms following strongyloidiasis treatment should raise possibility that initial ivermectin treatment was not fully curative (Pacanowski *et al*, 2005).

Decreasing titers of antistrongyloides antibodies was useful to assess treatment adequacy of treatment; by repeating serology at 3 to 6 months, as strongyloidiasis significantly reduced blood eosinophilia and serologic antibody titer after an average of 96 & 270 days, respectively (Kobayashi *et al*, 1994). In Cambodian refugees' patients (65%), followed with serial serology reached levels consistent with cure 6 to 12 months after treatment. Eosinophilia persisted for several months post treatment suggested either failure of treatment and/or other etiologies for the eosinophilia (Biggs *et al*, 2009).

The prognosis of strongyloidiasis is good except in the hyperinfection syndrome. The latter patients have high case-fatality rates increased by concomitant immunosuppression, bacteremia, and delayed diagnosis (El Masry and O'Donnell, 2005). Ivermectin failure raised possibility that patient has the underlying HTLV-1 (Jeyamani *et al*, 2007).

Prevention & Control (CDC, 2018): The best way to prevent *Strongyloides* infection is to wear shoes when you are walking on

soil, and to avoid contact with fecal matter or sewage. Proper sewage disposal and fecal management are keys to prevention.
Furthermore, if you believe that you may be infected, the best way to prevent severe disease is to be tested and, if found to be positive for disease, treated.

One should discuss testing with his or her doctor if on: 1-Taking steroids or other immunosuppressive therapies, 2- To start taking steroids or other immunosuppressive therapies, 3- A veteran who served in the South Pacific or Southeast Asia, 4- Diagnosed with cancer 5- Infected with human T-cell lymphotropic virus-1 (HTLV-1), and 6- Going to donate or receive organ transplants.

Nursing role: Standard precautions should be done for hospitalized strongyloidiasis patients. Wearing gloves and gowns, good hygiene, and diligent hand-washing is a must when in contact with the patient's feces. Of note, though persons with HIV/AIDS can disseminate strongyloidiasis or hyperinfection syndrome, observational studies did not cause an increased risk in such population.

Generally speaking, the association between the parasitic infections and human cancers are well-evidence. Three carcinogennic mechanisms were proved for the blood flukes; *Schistosoma haematobium, S. mansoni* and *S. japonicum* (Emilio, 2007). Infections in general can initiate or promote carcinogenesis by any of the 3 main mechanisms: chronic inflammation due to prolonged persistence of infectious agent in the host with the release of reactive oxygen radicals and reactive nitrogen radicals having the potential to damage DNA; insertion of active oncogene in host genomes (mechanism associated with oncogenic viruses, as HBV & HCV) and reduced immunosurveillance as a result of immunosuppression (Kuper *et al*, 2000). Also, liver flukes as *Clonorchis sinensis, Opisthorchus felineus* and *O. viverrini* cause cholangiocarcinoma in about ten percent of cases where millions are infected worldwide mostly asymptomatic but require treatment (El-Sayed et al, 2019).

Conclusion

Strongyloidiasis is one of the difficult parasitic diseases to diagnose due to absence of distinctive ova in stools, a low parasite load, rarity of rhabditiform larvae in stool, and asymptomatic presentation and/or nonspecific symptoms particularly in uncomplicated patients. Hence, it remains an underestimated public health problem. The chronic inflammation, metabolic oxidative stress induced by parasite-derived products and host tissue damage during parasite development, along with the active wound healing mechanisms by which *S. stercoralis* induce malignancy together with HTLV-1 and/or directly induce carcinogenesis must be considered.

Recommendations

1- For diagnosis, at least two concentrated stool specimens be examined for rhabditiform larvae as well as serologic testing. If the diagnostic tests are negative and clinical suspicion of strongyloidiasis remains, recommend either examination of duodenal fluid for larvae or empiric ivermectin therapy.
2- Ivermectin treatment for uncomplicated strongyloidiasis recommended (Grade 1A), dose of 200mcg/kg administered in two single doses, usually given two weeks apart.
3- In patients with disseminated disease (hyperinfection syndrome), extended dosing of ivermectin suggested (Grade 2C), typical dose schedule of 200mcg/kg daily for five to seven days minimum.
4- Ivermectin can also be combined with albendazole. Daily stool examinations must be performed during treatment to determine the effect on larval burden, and ongoing daily treatment until symptoms resolve and stool tests have been negative for at least two weeks is often recommended. In patients with eosinophilia persisted for more than three months despite therapy, one must recommend evaluation for treatment failure or other causes of eosinophilia.

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