Strongyloidiasis Associated With Human T-Cell Lymphotropic Virus Type I Infection in a Nonendemic Area

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Concomitant strongyloidiasis and human T-cell lymphotropic virus type I (HTLV-I) infection has been reported from areas in Japan where both organisms are endemic. We present four cases of concomitant infection with these organisms from an area that is not endemic for Strongyloides stercoralis. Three of the four patients had adult T-cell leukemia, an aggressive neoplasm resulting from HTLV-I infection, while the other was an asymptomatic carrier of HTLV-I. Three of the patients had spent their childhoods in an endemic location for both organisms, suggesting an initial infection at that time. Three patients were symptomatic from their parasitism. We conclude that strongyloidiasis may be found in nonendemic locations in patients with either adult T-cell leukemia or an asymptomatic HTLV-I carrier state. Whether infestation with this parasite contributes to the leukemogenesis of HTLV-I, as postulated by others, cannot at this time be determined.


Strongyloidiasis is an intestinal infection caused by Strongyloides stercoralis. Infection is thought to be acquired in most cases by transcutaneous penetration by the larvae, but in rare instances by sexual contact or the ingestion of contaminated food may also occur.1 The disease has a worldwide distribution, with a higher prevalence in tropical areas. It is found in 0.4% to 4% of residents in the southeastern United States and may also be found in rural areas and mental institutions.2,3 In nonendemic locations, such as Hawaii, S stercoralis is most commonly found in immigrant populations.4

Clinical infection is usually characterized by chronic relapsing gastrointestinal symptoms including nausea, vomiting, dyspepsia, bloating, and diarrhea, although as many as a third of patients may be asymptomatic.3 Long-standing carrier states are often observed, with the recovery of S stercoralis 20 to 30 years following a move away from the endemic site of the initial infection.1,5 A syndrome of hyperinfection with disseminated disease and a high mortality rate may be encountered in immunocompromised hosts.6-8

Human T-cell lymphotropic virus type I (HTLV-I) is a human retrovirus that has been linked etiologically to adult T-cell leukemia (ATL), a neoplasm of T-cell origin. In Okinawa, a prefecture in southern Japan, a high prevalence of antibodies to HTLV-I has been found in patients with strongyloidiasis.9 Conversely, in patients from Okinawa with HTLV-I infection, there is a significantly higher prevalence of S stercoralis carriers when compared to background population rates.10

To further understand the relationship between these organisms, we identified and retrospectively reviewed four cases of strongyloidiasis associated with either HTLV-I infection or ATL. These patients were unusual in that they all resided in Hawaii, an area previously shown to have a low prevalence of strongyloidiasis.4

Subjects and Methods

Patients were identified from either the hematology practice of one of us (J.M.N.) or from a retrospective review of clinical cases at the Kuakini Medical Center, Honolulu. The patients in cases 3 and 4 were not able to be tested for antibody to HTLV-I but were previously reported to have high-grade T-cell lymphomas, in one case consistent with ATL.11

The diagnosis of S stercoralis infestation was made on freshly collected specimens of either stool (cases 3 and 4), gastric aspirate (case 1), or postmortem histologic specimens of small bowel (case 2).

In cases 1 and 2, serum was studied by an enzyme-linked immunosorbent assay (ELISA) (Biotech Research Laboratories, Inc, Rockville, Md) for HTLV-I antibodies, and HTLV-I antibody positivity was confirmed by Western blot assay (Biotech Research Laboratories, Inc, Rockville, Md). All specimens were run in duplicate and under standard conditions.

Report of Cases

Case 1

A 71-year-old man of Japanese ancestry presented with dyspepsia, an 8-kg (18-lb) weight loss, Hemoccult-positive stools, hypoalbuminemia, and an elevated serum alkaline phosphatase level. Although born in Hawaii, he had lived in Okinawa from age 2 to age 19. He had otherwise been healthy except for a past episode of nephrolithiasis. An abdominal computed tomographic scan had been done and showed no abnormalities. An esophagastroduodenoscopy was performed and showed no abnormalities.
revealed mild proximal duodenitis. Biopsy specimens from the involved mucosa showed mild focal villous atrophy, with a large amount of *Strongyloides stercoralis* present, including both filariform and rhabdoid larvae. The patient was treated with a course of thiabendazole, with subjective clinical improvement. He has since been found to be HTLV-I antibody-positive.

**Case 2**

The patient, a 68-year-old Hawaiian-born woman of Japanese ancestry, was seen because of lethargy, anorexia, weight loss, and fevers. On examination she had diffuse lymphadenopathy, and a subsequent biopsy specimen showed diffuse large-cell non-Hodgkin’s lymphoma (T-cell immunoblastic sarcoma). She was found to have the antibody to HTLV-I by both ELISA and Western blot assay. She received several courses of chemotherapy consisting of BACOP (bleomycin sulfate, doxorubicin [Adriamycin] hydrochloride, cyclophosphamide, vincristine sulfate [Oncovin], and prednisone) and later M-BACOD (bleomycin, doxorubicin, cyclophosphamide, methotrexate, and dexamethasone), but her condition continued to deteriorate and she had recurrent infections. Hypercalcemia later developed, requiring the administration of plicamycin (previously called mithramycin) for its control. After a prolonged hospital course, she died of a *Staphylococcus aureus* pneumonia. An autopsy showed an aggressive T-cell immunoblastic sarcoma and clinically unsuspected parasitism of the small bowel with *S. stercoralis*.

**Case 3**

The patient, a 58-year-old Japanese man who was initially seen in 1964 with weight loss, anorexia, and mild diarrhea, was found by examination of fresh stool to have *S. stercoralis* infestation. He had been born in Okinawa but had later immigrated to Hawaii. He was initially treated with gentian violet but because he failed to improve, he was readmitted to hospital. On readmission, the patient was found to have spiking fevers, mild leukocytosis, and diffuse patchy infiltrates on a chest roentgenogram. A sputum specimen showed *S. stercoralis*, and an upper gastrointestinal study disclosed a dilated duodenal bulb. In the hospital the patient had confusion from hypercalcemia, which was successfully managed with the use of corticosteroids. He subsequently died of complications related to a liver biopsy and acute renal failure. The necropsy report initially suggested a systemic inflammatory process of undefined origin; on review, however, the histologic examination showed a diffuse high-grade lymphoma (pleomorphic immunoblastic sarcoma, T-cell type).

**Case 4**

A 57-year-old Japanese man was admitted to our hospital in 1961 with anorexia, low-grade fevers, weight loss, and diffuse adenopathy. Born in Okinawa, he later immigrated to Hawaii. While in the hospital, a fresh stool examination showed *S. stercoralis*. A lymph node biopsy specimen showed an acute lymphoma, diffuse type, and the patient was initially treated with mechlorethamine hydrochloride. He later died of this lymphoma. Retrospective review of the antemortem lymph node biopsy specimen revealed a high-grade lymphoma (pleomorphic immunoblastic sarcoma, T-cell type). No serum calcium levels were evaluated, and an autopsy was not done.

**Results**

The mean age of the four patients at the time the diagnosis of strongyloidiasis was established was 64 years. All four persons were known to have strongyloidiasis, three with gastrointestinatal symptoms and one clinically unsuspected. The most common symptoms reported were anorexia, mild diarrhea, weight loss, and dyspepsia.

The diagnosis of strongyloidiasis was established from an examination of fresh stool in two patients and from gastric aspirate in one patient. The fourth patient (case 2), who remained asymptomatic from the standpoint of his strongyloidiasis, was found at autopsy to have a massive load of the parasite in her small bowel.

Three of the four patients had presumably acquired strongyloidiasis at an early age while living in Okinawa, an area endemic for *S. stercoralis*. The fourth (case 2) had had no travel history to an area endemic for *S. stercoralis*.

Two of the patients (cases 3 and 4) did not have documented HTLV-I infection, but because they were originally from Okinawa and appeared to have ATL, it is probable that they were carriers of HTLV-I. Unfortunately, family members are not available for testing. The other two patients had documented HTLV-I antibodies. One of these patients died of ATL (case 2), but the other remains asymptomatic from the standpoint of his HTLV-I infection (case 1). The latter could have acquired HTLV-I infection in Hawaii, from his Okinawan parents, or while living in Okinawa from age 2 through 19. One patient (case 2) appears to have acquired both HTLV-I and *S. stercoralis* in Hawaii. She, too, is of Okinawan ancestry.

Hypercalcemia was present in two of the three patients with ATL. Both patients had symptoms attributed to hypercalcemia and required treatment to lower their serum calcium levels. The asymptomatic HTLV-I antibody-positive patient (case 1) did not have hypercalcemia.

A summary of the clinical characteristics of the four patients is given in Table 1.

**Discussion**

Human T-cell lymphotropic virus type I is a type C human retrovirus that was first identified by Poiesz and colleagues in a patient with a cutaneous T-cell malignant neoplasm. It has since been found to be related etiologically to ATL, a T-cell malignant disorder often associated with an

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**TABLE 1.—Characteristics of Patients With Strongyloidiasis and HTLV-I Infection or Adult T-Cell Leukemia (ATL)**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex Birthplace</th>
<th>HTLV-I Status</th>
<th>ATL</th>
<th>Hypercalcemia</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71</td>
<td>1964 Hawaii</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Dyspepsia</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>1964 Hawaii</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>3</td>
<td>58</td>
<td>1964 Okinawa</td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
<td>Anorexia, weight loss, mild diarrhea</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>1964 Okinawa</td>
<td>Unknown</td>
<td>Yes</td>
<td>No</td>
<td>Anorexia, weight loss, mild diarrhea</td>
</tr>
</tbody>
</table>

HTLV-I = human T-cell lymphotropic virus type I
aggressive clinical course, symptomatic hypercalcemia, and frequent cutaneous leukemia cell infiltrates. In addition, an asymptomatic carrier state, a preleukemic state (pre-ATL), and occasionally a chronic or smoldering form of ATL may also be observed in patients infected with the virus. More recently, HTLV-I has also been associated with other syndromes, including tropical spastic paraparesis and possibly thrombotic thrombocytopenic purpura.14-17

The virus is found to be endemic in geographically restricted areas in southern Japan, the Caribbean islands, Africa, South America, and in the southeastern United States. It has been found in as many as 9% of intravenous drug users in New York and, therefore, appears to be spreading in a population also at risk for acquiring human immunodeficiency virus infection.13,18 Viral transmission occurs by several means, including sexual intercourse, the transfusion of contaminated cell-containing blood products, ingestion of breast milk from mothers who are virus carriers, and the sharing of contaminated needles by intravenous drug users. There is also familial clustering of HTLV-I, suggesting both horizontal and vertical transmission of the virus.11,19,20

Current estimates indicate that ATL will eventually develop in fewer than 0.2% of those infected.21,22 Those carriers of the virus in whom adult T-cell leukemia has not yet developed are found to have polyclonal integration of HTLV-I proviral DNA in their lymphocytes. Once monoclonal integration of HTLV-I proviral DNA occurs, however, either pre-ATL, the smoldering or chronic form of ATL, or overt ATL is found.10,13 The only clinical disorder known to occur while the virus is still integrated in a polyclonal fashion is tropical spastic paraparesis, and this appears to be rare.

It is well known that S. stercoralis infestation is a chronic illness that, because of the organism's unusual life cycle, can persist with or without symptoms for many years after a person leaves an endemic area.1,5 It is therefore probable that three of our patients may have been harboring S. stercoralis since their childhoods in Okinawa. As noted, these three patients all had mild gastrointestinal symptoms, but a fourth patient was asymptomatic from the standpoint of her strongyloidiasis.

Studies from endemic areas have noted the coexistence of strongyloidiasis and ATL or HTLV-I infection.5,23 In Okinawa, 60% of patients with strongyloidiasis were found to have HTLV-I antibody, compared with only 20% of those without strongyloidiasis.2 Of 36 patients with both HTLV-I and strongyloidiasis, 14 (39%) were found to have monoclonal integration of HTLV-I proviral DNA in their lymphocytes.10 In that study, monoclonality was associated with the presence of abnormal circulating lymphocytes, an increased CD4:CD8 ratio, clinically smoldering ATL, and somewhat more severe symptoms of strongyloidiasis.10

Several possibilities may explain the concurrent infection with these organisms. One is that infection with HTLV-I causes defective T-cell function and that the resultant cell-mediated immunodeficient state may predispose to both infection with S. stercoralis and toward the progression of this infection to a hyperinfective stage.

Cell-mediated immunity has been found to be defective in patients with either an HTLV-I carrier state or ATL, and these patients may be at risk for several opportunistic infections, including Pneumocystis carinii pneumonia and disseminated fungal infections.24-26 In addition, other studies have shown that patients with defective T-cell function are predisposed to strongyloidiasis and that pre-existing strongyloidiasis may be converted to a hyperinfective stage with the onset of another unrelated immunosuppressive disease.7,8,27 We postulate that our patients with ATL or HTLV-I are more likely to acquire strongyloidiasis and if already infected with this organism, symptoms are more likely to develop that would lead to the diagnosis of parasitism.

Another explanation that has been suggested by a group of investigators in Okinawa20,23 is that chronic infestation with S. stercoralis may predispose to infection with HTLV-I and may act as a cofactor in the leukemogenesis of the virus. In the United Kingdom, studies of former Far East prisoners of war have shown that long-standing strongyloidiasis may cause generally impaired immunity and an increased risk of acquiring tuberculosis.28 Whether these patients are also at an increased risk of acquiring retroviral disease has not been determined.

Those patients studied in Okinawa with concomitant HTLV-I and strongyloidiasis were more likely to have ATL than the group with only HTLV-I infection.10 This has led these investigators to suggest S. stercoralis as a possible cofactor in the leukemogenesis of HTLV-I.10,23 Other organisms, including filariasis and malaria, have also been suggested as potential cofactors in the development of ATL.29,30 It seems plausible that prolonged antigenic stimulation induced by chronic parasitic infection may lower a host's immune response, reactivating a latent virus infection with a progression of polyclonal to monoclonal T-cell proliferation. A better understanding of the factors influencing HTLV-I-related leukemogenesis is needed to further evaluate these hypotheses.

Although unlikely, it remains possible that S. stercoralis itself may be a vector of HTLV-I. This has not yet been investigated.

We have described four patients with either an asymptomatic HTLV-I carrier state or ATL who have had concomitant strongyloidiasis. This had not previously been described in an area that is not endemic for S. stercoralis. The persistent parasitism seen in these patients is not surprising in view of previous studies on migrant populations; in these patients, however, this may also reflect an immunosuppressant effect of HTLV-I infection or ATL. We suggest that those patients known to have HTLV-I infection or HTLV-I-associated disease should be screened closely for the development of symptoms suggestive of strongyloidiasis. Whether routine stool examinations should be done to screen for asymptomatic strongyloidiasis in HTLV-I-infected patients is not known at this time. We recommend further studies on both the role that persistent parasitism plays with respect to the leukemogenesis of HTLV-I and on the immunomodulating effect of this virus on the human host.

REFERENCES
40:145-148


Clinical associated with WESTERN JOURNAL HTLV-II: Evolving Med 1981; 294:268-271

HTLV-I in carriers 1981; 2:517-522

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