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REDUCED EFFECT OF CHEMOTHERAPY OF STRONGYLOIDIASIS IN PATIENTS WITH CONCURRENT HTLV-I INFECTION IN OKINAWA, JAPAN

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Abstract: The effect of concurrent HTLV-I infection on the efficacy of anti-*Strongyloides* chemotherapy has been tested in a prognostic study on 96 patients with uncomplicated strongyloidiasis. The efficacy of treatment with pyrvinium pamoate and thiabendazole was found to be significantly low in the HTLV-I seropositive patients, as compared to that in the seronegative group. The cure rates in the HTLV-I seropositive patients, when assessed by both faecal examination and serological testing, were only 8.6% for pyrvinium pamoate treatment and 35.0% for thiabendazole treatment. On the other hand, the cure rates were 31.3% for pyrvinium pamoate treatment and 57.1% for thiabendazole treatment in the seronegative group.

Although antibody response against *Strongyloides* did not decrease among the HTLV-I seropositive patients, the total serum IgE levels, as well as eosinophil counts in peripheral blood, were relatively low in the seropositive group. Abnormal lymphocytes were demonstrated in 38.5% of the patients with concurrent HTLV-I infection. The presence of abnormal lymphocytes, however, appeared not to correlate with the therapeutic efficacy. A possible connection between the poor efficacy and depressed immune responses provided by the concurrent HTLV-I infection is discussed. The low efficacy in the HTLV-I seropositive patients also provides a causal explanation for the significant accumulation of patients with concurrent HTLV-I infection in Okinawa.

INTRODUCTION

Strongyloidiasis caused by *Strongyloides stercoralis* infection still remains prevalent in Okinawa Prefecture, Japan, where other parasitic diseases have been almost entirely eradicated in recent years (Sato, 1986). Because of its opportunistic nature, the great majority of patients who are immunocompetent are generally chronic, producing no symptom clearly attributable to the presence of the parasite. On the other hand, under the condition of depressed immune competence, the chronic infection progresses to a massive and often fatal systemic infection as a consequence of increasing autoinfection with larval parasites.

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Okinawa Prefecture is also known to be an endemic area for human T-cell leukemia virus (HTLV-I) infection (Clark *et al.*, 1985). The HTLV-I is aetiologically associated with adult T-cell leukemia (ATL) which leads to severe deficiencies in immunological responses. Recently, it has been demonstrated that the patients with an asymptomatic *Strongyloides* infection in Okinawa are highly accompanied by the ATL viral infection (Nakada *et al.*, 1984; Fujita *et al.*, 1985; Sato and Shiroma, 1989). Under the condition of concurrent *Strongyloides* and ATL viral infection, the progression of asymptomatic *Strongyloides* infection to a fatal disseminated state has been often observed among the patients who developed ATL (Takara *et al.*, 1980; Matsui *et al.*, 1982; Oura *et al.*, 1986). A possible explanation for the high frequency of such a complication, however, has not yet been offered. In this paper we present results showing the depressed efficacy of treatment of strongyloidiasis in patients with concurrent HTLV-I infection and thus discuss the possibility that the low therapeutic efficacy may be attributed to the depressed immune responses provided by the viral infection and also may be responsible for a significant accumulation of strongyloidiasis patients with concurrent HTLV-I infection for a long period in Okinawa.

Materials and Methods

Patients

A total of 96 patients with strongyloidiasis received medical treatment for strongyloidiasis in the Izumizaki Hospital, Okinawa, Japan. They were consisted of 47 males and 49 females. Their age ranged from 30 to 74 years (mean=53.3 years). They were asymptomatic or mildly symptomatic cases. Among them, positive rate of antibodies against ATL-associated antigen (ATLA) was as high as 67.7%.

Treatments

Fifty-one patients were treated with pyrvinium pamoate suspension (Poquil), which was administered in a dosage of 5 mg per kg body weight daily for 3 to 5 consecutive days. For the other 27 patients, thiabendazole (25 mg/kg for 4 days) was administered. The above treatment schedules have long been used in Okinawa for treatment of strongyloidiasis. The remaining 18 patients were left without any treatment as a control group. The duration from treatment to follow-up faecal examination was different for each cases, but it was more than 2 years for all cases.

Faecal examination

The follow-up faecal examination after the treatment was performed repeatedly for consecutive 3 days by three different method, e.g. direct faecal smear, formol-ether concentration method and faecal culture (Harada-Mori method).

Antibodies to *S. stercoralis*

In order to assess serologically the efficacy of treatment, the serum antibodies to *S. stercoralis* were measured by an enzyme-linked immunosorbent assay (ELISA). The antigens used were prepared from *S. stercoralis* filariform larvae collected from faeces of strongyloidiasis patients (Sato *et al.*, 1983). The conventional technique for the micro-ELISA using a microtiter plate was the same as that described in a previous paper (Sato *et*

al., 1985). The sera were tested at a single dilution of 1:50 and the intensity of antibody response was expressed as the absorbancy (OD) at 500 nm. On the basis of the previous criteria, the OD value of over 0.5 was regarded as being antibody positive (Sato *et al.*, 1990b).

Detection of antibody to ATL virus

The individuals having anti-ATLA antibodies have been known to be infected with HTLV-I in their peripheral lymphocytes (Gotoh *et al.*, 1982).

A kit for the particle agglutination test to detect anti-ATLA antibodies was kindly supplied from Fujirebio Inc., Tokyo. A usual indirect agglutination test using gelatin particles coated with antigens prepared from culture fluid of the virus-producing cell line was done in U-bottomed wells of a plastic microplate (Ikeda *et al.*, 1984). The mixtures of the antigen-coated particles and serially diluted sera in the wells were allowed to stand for 3 hr at room temperature and the resulting patterns formed on the bottom of the wells were read. The final serum dilution of 1:16 or higher showing agglutination was interpreted as positive.

Serum total IgE

Serum IgE was measured by a standard radioimmunosorbent test using Phadebas IgE test kit (PRIST; Pharmacia Fine Chemicals, Uppsala, Sweden). Serum IgE levels were expressed in ng/m*l* of serum, assuming that 1 unit/m*l* corresponds to approximately 2 ng/m*l*.

Haematological examinations

Eosinophils from peripheral blood were counted in Wright's-stained smear and were reported as percentage in 100 leukocytes. Morphologically abnormal lymphocytes having lobular or indented nulei were also counted in the same smears.

Statistics

The data were analyzed by χ^2 test and Student's t test, as appropriate. A P value of more than 0.05 was considered not to be significant.

RESULTS

The results of follow-up examination after treatment are shown in Table 1. The total cure rates, as estimated by both faecal and serological examinations, were 15.7% for pyrvinium pamoate treatment and 40.7% for thiabendazole treatment, respectively. Although three patients in the untreated group were negative in the follow-up faecal examination, they were serologically equivocal for complete cure and the spontaneous cure determined by exclusion of the equivocal cases was not detected in the untreated group. When the efficacy were compared between the HTLV-I seropositive and seronegative patients, the cases with complete cure were significantly fewer in the HTLV-I seropositive group than in the seronegative group in both treatments.

Table 2 represents total IgE levels in sera of 39 patients who were still positive after the treatment. The IgE levels were relatively lower in the HTLV-I seropositive group than in the seronegative group. Although the difference was not significant statistically, the mean IgE level in the seropositive group was as low as one-third that of the seronegative group.

Table 1 Effect of concurrent HTLV-I infection on treatment of strongyloidiasis with pyrvinium pamoate and thiabendazole

Treatment	Anti-ATLA antibody	No. examined	Faecal examination: Positive (not cured)	Faecal examination: Negative: Sero-positive† (equivocal)	Faecal examination: Negative: Sero-negative† (cured)	Significance*
Pyrvinium pamoate	Positive	35	30 (85.7)	2 (5.7)	3 (8.6)	P<0.05
	Negative	16	10 (62.5)	1 (6.3)	5 (31.3)	
	Total	51	40 (78.4)	3 (5.9)	8 (15.7)	
Thiabenda-zole	Positive	20	9 (45.0)	4 (20.0)	7 (35.0)	N.S.
	Negative	7	2 (28.6)	1 (14.3)	4 (57.1)	
	Total	27	11 (40.7)	5 (18.5)	11 (40.7)	
Untreated	Positive	10	7 (70.0)	3 (30.0)	0 (0)	N.S.
	Negative	8	8 (100)	0 (0)	0 (0)	
	Total	18	15 (83.3)	3 (16.7)	0 (0)	

*Significance between HTLV-I seropositive and seronegative groups; †anti-*Strongyloides* antibody

Although the difference of cure rate between HTLV-I seropositive and seronegative groups was not significant ($P<0.1$) in thiabendazole treatment, the total cure rate of both treatments was significantly lower ($P<0.05$) in the HTLV-I seropositive group.

Table 2 Comparison of serum total IgE levels between HTLV-I seropositive and seronegative patients

IgE level (ng/ml)	Anti-ATLA antibody: Positive (n=38)	Anti-ATLA antibody: Negative (n=12)	
<1,000	34 (89.5)	8 (66.7)	
1,000 - 3,000	4 (10.5)	2 (16.7)	
3,100 - 5,000	0 (0)	1 (8.3)	
>5,000	0 (0)	1 (8.3)	
Mean±SD	415.8±523.2	1,300±1,795	N.S.*

*Significance between HTLV-I seropositive and seronegative groups.

Table 3 also shows eosinophil counts in peripheral blood of 25 patients with *Strongyloides* infection. Eosinophilia of over 6% was detected in 57.8% of patients who were negative for anti-ATLA antibody, while the percentage of patients with eosinophilia was 35.0% in the HTLV-I seropositive patients. On the other hand, when anti-*Strongyloides* antibodies were compared between the HTLV-I seropositive and seronegative groups, the antibody levels were relatively higher in the seropositive group, showing no depressed antibody response to *Strongyloides* among the seropositive group (Fig. 1).

The presence of abnormal lymphocytes in peripheral blood was determined in 52 patients who were positive for anti-ATLA antibody and atypical lymphocytes were detected in 20

Table 3 Eosinophil counts in peripheral blood of strongyloidiasis patients with or without concurrent HTLV-I infection

Blood eosinophils (%)	Anti-ATLA antibody		
	Positive (n=40)	Negative (n=19)	
-6	26 (65.0)	8 (42.1)	
7-10	7 (17.5)	7 (36.8)	
11-15	6 (15.0)	2 (10.5)	
16-	1 (2.5)	2 (10.5)	
Eosinophilia (>6%)	14 (35.0)	11 (57.8)	N.S.*

*Significance between HTLV-I seropositive and seronegative groups.

(38.5%) patients. The relation between the presence of atypical cells and the therapeutic efficacy is shown in Table 4. The positive rate of atypical cells was relatively higher in the group of unsuccessful treatment than in the group of complete cure in pyrvinium pamoate treatment, but it were almost similar in thiabendazole treatment.

Discussion

Strongyloidiasis and ATL are presently highly prevalent in Okinawa Prefecture, Japan; the prevalence levels appear to be 5 to 10% for *Strongyloides* (Sato, 1986; Sato *et al.*, 1990b) and about 20% for HTLV-I infection (Clark *et al.*, 1985). Recently, it has been pointed out by several researchers that *Strongyloides* carriers in Okinawa are frequently accompanied by HTLV-I infection (Nakada *et al.*, 1984; Fujita *et al.*, 1985; Sato and Shiroma, 1989). In these studies, the positive rates of anti-ATLA antibody as high as

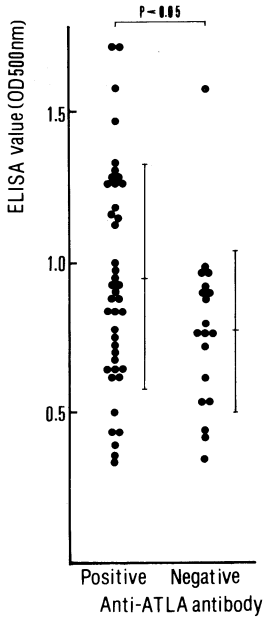

Figure 1 Comparison of anti-*Strongyloides* ELISA values between HTLV-I seropositive and seronegative patients with strongyloidiasis.

Table 4 Correlation between efficacy of treatment and presence of abnormal lymphocytes in peripheral blood of patients with concurrent HTLV-I infection

Treatment	Efficacy of treatment			Total
	Not cured	Equivocal	Cured	
Pyrvinium pamoate	13/28 (46.4)	0/2 (0)	1/3 (33.3)	14/33 (42.4)
Thiabendazole	3/9 (33.3)	1/3 (33.3)	2/7 (28.6)	6/19 (31.6)
Total	16/37 (43.2)	1/5 (20.0)	3/10 (33.3)	20/52 (38.5)

No. positive/No. examined (%)

57.8 to 73.6% were detected among the strongyloidiasis patients.

Several explanations have been proposed for the severe complication of these infections. The participation of antigenic components common to *Strongyloides* and ATLA which may produce high positive rate of anti-ATLA antibody among the *Strongyloides* carriers has been excluded by the authors (Sato and Shiroma, 1989). Possible participation of any epidemiological factors to produce the severe overlap of the two infections has also been excluded in a previous paper (Sato *et al.*, 1990a).

Alternatively, it can be supposed that the concurrent HTLV-I infection may affect on the severity of *Strongyloides* infection through the depressed immune competence of host during the viral infection. The data presented in this paper demonstrate that the anti-parasitic effect of the anthelmintics is greatly reduced in strongyloidiasis patients with concurrent HTLV-I infection. In Okinawa, intractable cases of strongyloidiasis, in which relapse occurs repeatedly after various treatment over a period of many years, have been often observed (Shiroma *et al.*, 1990). Although the factor responsible for such a resistance to anthelmintic treatment is unclear, it can be postulated that the poor efficacy of treatment may be attributed to the depressed immune response which provided by the viral infection. As well documented, ATL is characterized by an unique T-lymphocyte malignancy which leads to severe deficiencies in immune responses, and it is also known that the disorder to a T-cell mediated immune system has already begun in the stage of virus carriers (Imai and Hinuma, 1983; Yasuda *et al.*, 1986; Tanaka *et al.*, 1989; Prince *et al.*, 1990). Because of the opportunistic nature of the parasitic pathogen, it is reasonable to suppose the immune dependence of anti-parasitic chemotherapy in strongyloidiasis.

In the past decade, substantial evidence for the immune dependence of chemotherapy has accumulated. It has been known that immunosuppression reduces the efficacy of chemotherapy in several parasitic diseases, such as malaria (Lwin *et al.*, 1978), trypanosomiasis (Frommel, 1988), onchocerciasis (Bianco *et al.*, 1986) and schistosomiasis (Doenhoff and Bain, 1978). In the case of strongyloidiasis, it is also well documented that the patients with severe infection under the immunocompromised condition often fail to respond to anthelmintic treatment, and that repeated courses of treatment are necessary to obtain a complete cure for such a severe case (Scowden *et al.*, 1978; Weller *et al.*, 1981; Shelhamer *et al.*, 1982; Morgan *et al.*, 1986). Although the immune factor involved in influencing the drug efficacy is not yet determined, it has been reported that antibodies specific for parasite, when it were administered simultaneously with drug, enhanced the efficacy of drug against schistosomes and malaria parasites (Doenhoff and Bain, 1978; Targett, 1985; Brindly and Sher, 1987). When the antibody titers to *Strongyloides* were compared between HTLV-I seropositive and seronegative patients in the present study, however, we could not find any evidence to suppose a depressed antibody response against *Strongyloides* in the seropositive group. While the drug efficacy in onchocerciasis reduced markedly in T-cell deprived mice but not in congenitally B-cell deficient mice, suggesting that cellular immune effector mechanism other than the serum antibody may contribute to the efficacy of chemotherapy in this parasitic disease (Bianco *et al.*, 1986). With respect to strongyloidiasis, significance of cell-mediated immunity in controlling and preventing *Strongyloides* infection has also been suggested in several clinicopathological studies (Purtilo *et al.*, 1974; Scowden *et al.*, 1978; Cohen and Spry, 1979). As already mentioned above, HTLV-I carriers are known to have immunological abnormalities, such as increased spontaneous lymphoproliferation, decreased mitogenic responses and

increased expression of IL-2 receptor on the surface of T lymphocytes. In the present study, morphologically atypical lymphocytes were detected in about 40% of HTLV-I seropositive patients examined. In their study on 36 patients, Nakada *et al.* (1987) has reported that abnormal lymphocytes, as well as monoclonal integration of HTLV-I proviral DNA, were detected in many patients and indicated that the presence of abnormal cells and monoclonal integration of proviral DNA correlated with a trend for greater severity of the parasitic infection. However, we could find no correlation between the presence of abnormal cells and the efficacy of treatment in the present study. On the other hand, it was noted that total serum IgE levels and eosinophil counts in peripheral blood were relatively low in the HTLV-I seropositive patients. The IgE and eosinophilic responses are well known to play an important role in protective immunity to parasitic helminths (Capron *et al.*, 1981; Dessein *et al.*, 1981; Kojima *et al.*, 1985). Recently, it was also demonstrated in a study with murine infection model that IL-5-dependent eosinophilic response was important for protective immunity to *Strongyloides* infection (Korenaga *et al.*, 1991). The relative decrease of IgE level and peripheral eosinophils in the HTLV-I seropositive patients may participate in the poor efficacy of chemotherapy. Further investigations on a possible connection between the immune responses and drug efficacy in strongyloidiasis should be intended.

Finally, the reduced efficacy of drug treatments in HTLV-I seropositive patients may provide another explanation for the high concurrency of HTLV-I. Due to resistance to anthelmintic treatments, which has long been used for strongyloidiasis in Okinawa, the patients with concurrent HTLV-I infection might harbour the infection for many years, resulting a significant accumulation of such patients.

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糞線虫症の治療効果に及ぼすATLウイルス混合感染の影響

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沖縄では糞線虫保有者の多くに，ATL病原ウイルスの混合感染が見られることが知られている。ATLウイルスの混合感染が，糞線虫に対する駆虫効果にどのような影響を与えているかについて，96名の糞線虫保有者を対象に検討した。治療はピルビニーム・パモエート（PP）とサイアベンダゾール（TB）を用いて行い，いずれの場合でもATLウイルスの感染が陽性である糞線虫保有者において，治療後の治癒率が著明に低いことを確認した。すなわち，ATLウイルス陽性者での治癒率は，PP治療でわずか8.6%，TB治療の場合で35.0%であったのに対し，ATLウイルス陰性の糞線虫保有者では，おのおの31.3%，57.1%であった。

これらの糞線虫保有者について，抗-糞線虫抗体値を比較したところ，ATLウイルス陽性群において抗体値が低いことを確認することはできなかったが，末梢血好酸球と血清総IgEレベルは，ATLウイルス陽性群において低い傾向が認められた。また，ATLウイルス陽性の対象者において，その約40%に異型リンパ球の出現を認めたが，異型リンパ球の存在と駆虫効果の間には特に関連を認め得なかった。かかる治癒率の低下は，ATLウイルスの感染による何らかの免疫低下状態によってもたらされた可能性と，これが長年にわたりATLウイルス陽性の糞線虫保有者を選択的に蓄積させ，今日の高い混合感染状態をもたらした，主要な原因である可能性が考えられた。

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