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CLINICAL RESEARCH

Endoscopic and histopathological study on the duodenum of *Strongyloides stercoralis* hyperinfection

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Abstract

AIM: To investigate endoscopic and histopathological findings in the duodenum of patients with *Strongyloides stercoralis* (*S. stercoralis*) hyperinfection.

METHODS: Over a period of 23 years (1984-2006), we investigated 25 patients with *S. stercoralis* hyperinfection who had had an esophagogastroduodenoscopy before undergoing treatment for strongyloidiasis. The clinical and endoscopic findings were analyzed retrospectively.

RESULTS: Twenty-four (96%) of the patients investigated were under immunocompromised condition which was mainly due to a human T lymphotropic virus type 1 (HTLV-1) infection. The abnormal endoscopic findings, mainly edematous mucosa, white villi and erythematous mucosa, were observed in 23 (92%) patients. The degree of duodenitis including villous atrophy/destruction and inflammatory cell infiltration corresponded to the severity of the endoscopic findings. The histopathologic yield for identifying larvae was 71.4% by duodenal biopsy. The endoscopic findings of duodenitis were more severe in patients whose biopsies were positive for larvae than those whose biopsies were negative (Endoscopic severity score: 4.86 ± 2.47 *vs* 2.71 ± 1.38, $P < 0.05$).

CONCLUSION: Our study clearly demonstrates that, in addition to stool analysis, endoscopic observation and biopsies are very important. We also emphasize that *S. stercoralis* and HTLV-1 infections should be ruled out before immunosuppressive therapy is administered in endemic regions.

Key words: *Strongyloides stercoralis*; Strongyloidiasis; Hyperinfection; Endoscopy; Histopathology; Duodenum

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INTRODUCTION

Strongyloides stercoralis (*S. stercoralis*) is an intestinal nematode which is a parasite of humans. About 100 million people are infected by this parasite in tropical and subtropical areas[1]. Infections are acquired when larvae penetrate the skin and migrate to the duodenum and upper jejunum to mature. An internal autoinfective cycle allows the parasite to reside within a human for years. Clinical syndromes of *S. stercoralis* vary widely. Chronic infection with *S. stercoralis* is most often asymptomatic. Hyperinfection describes a syndrome of accelerated autoinfection which results from immunosuppression. Detection of an increased number of larvae in stool, sputum and/or tissue is a hallmark of hyperinfection[2]. Gastrointestinal and pulmonary symptoms are common but non-specific, and include abdominal pain, diarrhea, vomiting, adynamic ileus, small bowel obstruction (SBO) and protein-losing enteropathy, as well as pneumonia. Disseminated infection is the migration of larvae to organs beyond the range of the autoinfective cycle (lungs and gastrointestinal tract) and is often complicated by Gram-negative sepsis. Such organs include the skin, liver, central nervous system as well as virtually every other organ. An immunocompromised condition consists of immunosuppressive drug therapy (e.g., corticosteroids, cyclosporine and anti-cancer drugs), hematologic malignancies, organ transplants, human T lymphotropic virus type 1 (HTLV-1) infection, and human immunodeficiency virus (HIV) infection[1,2]. As *S. stercoralis* colonizes in the duodenum where the larvae

mature, endoscopic evaluation has been recognized as an important tool for diagnosing strongyloidiasis. Although there have been several reports demonstrating endoscopic findings of strongyloidiasis, most of these are case reports or small case series[3-19]. This study aims at investigating the relationship of endoscopic markers to clinical and histopathological findings of the duodenum in patients with *S. stercoralis* hyperinfection in an endemic region.

MATERIALS AND METHODS

Patients

Over a 23-year period from 1984 to 2006, we identified 25 patients (15 males and 10 females; mean age = 63.0 ± 14.1 years) with *S. stercoralis* hyperinfection who had had an esophagogastroduodenoscopy (EGD) before undergoing treatment for strongyloidiasis at Ryukyu University Hospital and other affiliated hospitals in Okinawa, Japan. The diagnosis of *S. stercoralis* hyperinfection was based on gastrointestinal, pulmonary and/or systemic symptoms along with the identification of an increased number of *Strongyloides* larvae or ova in the stool, sputum, gastroduodenal drainage and/or tissue. The clinical and endoscopic findings of the patients were investigated retrospectively. The study was conducted and carried out in accordance with the Helsinki Declaration.

Endoscopy and histopathology

EGD was performed with forward-viewing endoscopes (Olympus, Tokyo, Japan) at the second portion of the duodenum. Since the endoscopic severity scoring system of the duodenum has not been established, we created the scoring system, which was determined by the total number of points for duodenitis. One point was given for a mild form (edema, erythema and white villi), two points for a moderate form (erosion, fine granule and hemorrhage) and three points for a severe form (ulcer, dilatation, dilatation and pseudopolyps). At endoscopy, biopsy specimens were obtained from the duodenal mucosa in a routine fashion using standard forceps. The specimens were stained with hematoxylin and eosin for histopathological evaluation. Duodenal pathology was assessed as described elsewhere[20].

Statistical analysis

Mann-Whitney *U*-test was used, when appropriate, to compare any differences among the groups. Statistical comparisons were analyzed using SPSS for Windows version 15 (SPSS Inc., Japan). *P* values less than 0.05 were considered statistically significant.

RESULTS

Clinical features

The clinical features of the patients are summarized in Table 1. The main symptoms and/or illnesses complicated by the hyperinfection were as follows: vomiting in 13 (52.0%), abdominal pain in 10 (40.0%), diarrhea in 8 (32.0%), SBO in 8 (32.0%), weight loss in 7 (28.0%), bacterial meningitis in 3 (12.0%), sepsis in 3 (12.0%), pneumonia in 2 (8.0%), and gastrointestinal bleeding in 2 (8.0%) patients. Most patients had more than one clinical symptom or illness. Six patients had disseminated infection (bacterial meningitis and/or sepsis) and the outcome of 2 patients was fatal. Twenty-four (96%) patients were under immunocompromised conditions resulting from HTLV-1 infection, administration of corticosteroid, diabetes mellitus, alcoholism, liver cirrhosis and chronic renal failure. Of note, 18 (72.0%) patients were HTLV-1 carriers. The diagnostic samples used for identifying *Strongyloides* were as follows: stool samples from 17 (68.0%) patients, duodenal biopsy from 15 (60.0%) patients, gastroduodenal drainage from 9 (36.0%) patients and sputum from 3 (12.0%) patients. Most patients were treated with thiabendazole or ivermectin alone and 2 patients needed a combination of the two drugs.

Endoscopic and histopathological findings

The endoscopic findings of the patients are summarized in Table 2. Gross abnormal findings were observed in 23 (92.0%) patients and normal findings in 2 (8.0%) patients. A broad range of endoscopic findings included edematous mucosa in 16 (69.5%) patients, white villi in 13 (56.5%), erythematous mucosa in 9 (39.1%), erosion in 6 (26.0%), stenosis in 4 (17.3%), fine granule in 4 (17.3%), hemorrhage in 3 (13.0%), dilatation in 3 (13.0%), and ulcer in 2 (8.6%) patients (Figure 1). Most patients had more than one finding. Strongyloidiasis was diagnosed histopathologically in 71.4% (15/21) of patients who had duodenal biopsies. According to the endoscopic severity score of the duodenum, the endoscopic findings of duodenitis were more severe in patients whose biopsies were positive for larvae than in those with negative biopsies (4.86 ± 2.47 *vs* 2.71 ± 1.38, $P < 0.05$, Figure 2). Representative endoscopic images of white villi and edematous mucosa (Figure 3), white villi and stenosis (Figure 4), and ulcer and pseudopolyps (Figure 5) are shown along with the histopathological findings. As shown together with the endoscopic and histopathological images, the degree of duodenitis, including villous atrophy/destruction and inflammatory cell infiltration, was associated with the severity of the endoscopic findings. In 6 cases whose stool was not obtained due to SBO or larvae were not identified in the stool, strongyloidiasis was diagnosed only by duodenal biopsies.

DISCUSSION

This study was conducted in the Okinawa islands, a subtropical region of Japan, where both *S. stercoralis* and HTLV-1 are endemic and epidemiological studies have been thoroughly conducted[21-24]. There is an increasing body of evidence regarding the strong association between *S. stercoralis* and HTLV-1 co-infection and hyperinfection syndrome[21-26], which has been further strengthened by our striking result that a majority (72%) of the patients with hyperinfection were co-infected with HTLV-1. We also confirmed the well-described role of corticosteroids in triggering hyperinfection regardless of the presence of HTLV-1 co-infection. Corticosteroids not only have a well-known effect impairing human immunity but also directly affect the female larvae to increase output of infective

Table 1 Clinical characteristics of patients with *S. stercoralis* hyperinfection

Case No.	Age/Gender	Presenting symptoms and/or illness	Immunosuppressive state	Diagnosis	Treatment	Outcome
1	51/M	Meningitis, GI bleeding	Alcoholism	Duodenal biopsy, stool	TBZ	Cured
2	72/M	Diarrhea	HTLV-1	Stool	TBZ	Cured
3	80/M	Sepsis, meningitis	HTLV-1, corticosteroids	Duodenal biopsy, stool, sputum, gastroduodenal drainage	TBZ	Cured
4	38/M	Abdominal pain	HTLV-1	Duodenal biopsy, stool	TBZ	Cured
5	58/F	Sepsis, diarrhea, pneumonia	Corticosteroids	Sputum	IVM	Dead
6	86/F	Vomiting, weight loss	HTLV-1, DM	Duodenal biopsy, stool, sputum	IVM	Cured
7	31/F	SBO, abdominal pain, vomiting	HTLV-1, alcoholism	Duodenal biopsy, stool, gastroduodenal drainage	TBZ	Cured
8	58/F	Vomiting, weight loss	HTLV-1	Duodenal biopsy, gastroduodenal drainage	IVM	Cured
9	62/M	Meningitis, diarrhea	HTLV-1, DM	Duodenal biopsy, gastroduodenal drainage	TBZ	Cured
10	73/F	Abdominal pain	HTLV-1, liver cirrhosis	Stool	IVM	Cured
11	58/M	SBO, abdominal pain, vomiting	HTLV-1, DM	Duodenal biopsy	IVM, TBZ	Cured
12	52/M	SBO, abdominal pain, vomiting	HTLV-1	Duodenal biopsy, stool, gastroduodenal drainage	TBZ	Cured
13	74/M	Diarrhea, weight loss	Chronic renal failure	Stool	IVM	Cured
14	66/F	Vomiting, diarrhea	HTLV-1	Duodenal biopsy, stool	TBZ	Cured
15	42/M	SBO, abdominal pain, GI bleeding	HTLV-1	Duodenal biopsy, stool	IVM, TBZ	Cured
16	56/F	Vomiting, abdominal pain	HTLV-1	Duodenal biopsy, gastroduodenal drainage	TBZ	Cured
17	62/M	SBO, abdominal pain, vomiting	None	Stool	TBZ	Cured
18	80/M	SBO, abdominal pain, vomiting	Alcoholism	Stool	IVM	Cured
19	82/M	SBO, meningitis, pneumonia	DM	Stool, sputum	IVM	Dead
20	57/M	Diarrhea, weight loss	HTLV-1	Stool	IVM	Cured
21	76/F	Vomiting, weight loss	HTLV-1	Duodenal biopsy, stool	TBZ	Cured
22	50/F	SBO, abdominal pain, vomiting	HTLV-1, corticosteroids	Duodenal biopsy	IVM	Cured
23	66/M	Vomiting, weight loss	HTLV-1	Duodenal biopsy, gastroduodenal drainage	IVM	Cured
24	71/M	Sepsis, diarrhea	Corticosteroids	Gastroduodenal drainage	IVM	Cured
25	74/F	Vomiting, diarrhea, weight loss	HTLV-1	Gastroduodenal drainage, stool	IVM	Cured

GI: Gastrointestinal; SBO: Small bowel obstruction; DM: Diabetes mellitus; TBZ: Thiabendazole; IVM: Ivermectin.

larvae with a structural similarity to larval ecdysteroids[1,27].

Enteritis by *S. stercoralis* has been studied since the early 1960's before the endoscopic era. de Paola *et al*[28] classified the histopathological changes in fatal cases into three forms: catarrhal enteritis, edematous enteritis and ulcerative enteritis. Catarrhal enteritis is a minor form characterized by mild mucosal congestion with larvae restricted to the mucous membrane. Edematous enteritis is a moderately serious form characterized by edematous thickening of the wall, swelling folds and villous atrophy. Larvae occupy lymph-vessel spaces. They also observed that mucosal edema was not only a result of inflammation and protein deficiency but also an effect of larval invasion in the lymph vessels and lymphangiectasia. Ulcerative enteritis is a serious form characterized by ulcers and fibrosis. Larvae are encountered in the entire wall. In the endoscopic era, there have been several case reports describing endoscopic findings of the duodenum in strongyloidiasis, including normal mucosa, edema, erythema, erosion, swollen folds, fine granule, tiny ulcer, polyps, hemorrhage, megaduodenum, deformity, and stenosis (Table 3). To our knowledge, the present retrospective study represents the largest endoscopic experience with *S. stercoralis* hyperinfection. In the histopathological studies, Coutinho *et al*[29] reported that duodenal villous atrophy and crypt hyperplasia were proportional to the degree of clinical severity of strongyloidiasis. Suarez and Sanchez[19] confirmed that plasma cell infiltration, villous atrophy and severe duodenitis were the characteristics of severe strongyloidiasis. A recent study clearly demonstrated that strongyloidiasis disrupted epithelial kinetics in the human small intestine by the induction of apoptosis and inhibition of cell proliferation, thereby resulting in villous atrophy and impaired barrier function[17]. Our observations disclosed that endoscopic findings of duodenitis were more severe in the patients whose biopsies were positive for larvae than in those with negative biopsies. Considering the fact that increased numbers of larvae are strongly associated with the progression to hyperinfection, our result supports their findings.

Prior reports have indicated that findings frequently include edematous mucosa, swollen folds and erythematous mucosa. However, pathognomonic findings are apparently not evident[3-19]. Our present study confirmed the aforementioned frequent findings. In addition, we noticed that an endoscopic feature of duodenal white villi seemed to be a frequent finding. The findings of tiny white spots[9] and white punctuate dotting mucosa[11] appear to be similar in appearance. The endoscopic finding of white villi is well-known in intestinal lymphangiectasia with protein-losing enteropathy. It represented markedly dilated lymphatics in the stroma of the villi and fats, including fat droplets in the absorptive cells from the impaired transport of fats from intestinal epithelial cells to intestinal lymphatics[30,31]. Considering the fact that larvae invade the lymph vessels and that there

Table 2 Endoscopic and histopathological findings of the duodenum

Case No.	Endoscopic findings of the duodenum	Histopathologic detection of *S. stercoralis* in the duodenum
1	Edema, erythema, erosion, hemorrhage	Larvae
2	Erythema	Negative
3	Edema, white villi, erosion	Larvae
4	Edema, white villi, erythema, dilatation	Larvae
5	White villi	ND
6	Edema, fine granule	Larvae
7	Erythema	Larvae
8	Edema, erosion, stenosis	Larvae
9	Edema, white villi	Larvae
10	Normal	ND
11	Edema, white villi, dilatation	Larvae
12	Edema, white villi	Larvae
13	White villi, erythema	Negative
14	Edema, white villi, fine granule	Larvae
15	Edema, erythema, ulcer, hemorrhage, pseudopolyps	Larvae
16	Edema, white villi, stenosis	Larvae
17	Edema, stenosis	Negative
18	White villi, erythema, erosion	Negative
19	Edema, ulcer	Negative
20	Normal	ND
21	Edema, white villi, erosion, hemorrhage	Larvae
22	Edema, white villi, erosion, fine granule, stenosis	Larvae
23	Fine granule, dilatation	Larvae
24	Edema, white villi, erythema	Negative
25	Erythema	Negative

Edema: Edematous mucosa; Erythema: Erythematous mucosa; ND: Biopsies were not done.

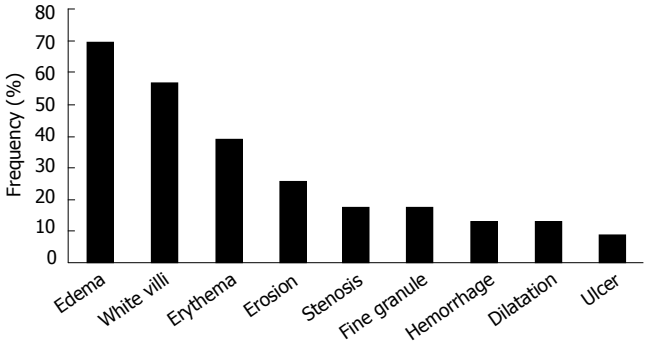

Figure 1 Frequency of abnormal endoscopic findings in the duodenum

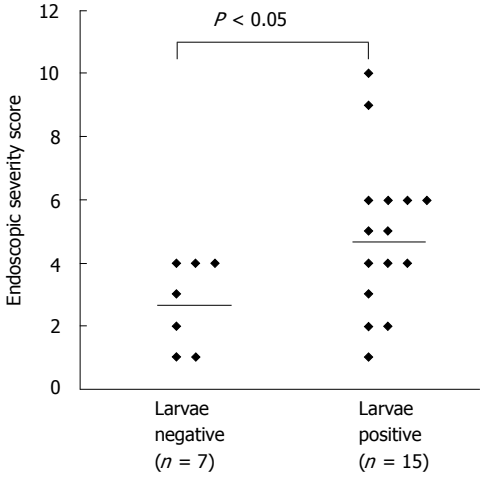

Figure 2 Comparison of endoscopic severity of the duodenum between the patients with larvae present and larvae absent in the duodenal biopsy ($P < 0.05$, Mann-Whitney *U*-test).

is subsequent lymphangiectasia in edematous enteritis as reported by de Paola *et al*[28], the appearance of white villi may reflect villous atrophy/destruction and mucosal edema similar to intestinal lymphangiectasia. We, therefore, emphasize that white villi can be a good endoscopic marker for strongyloidiasis in endemic regions.

There have been very few reports regarding the histopathologic yield by endoscopy for strongyloidiasis. In a study by Thompson *et al*[13], a minimum of six biopsies were obtained from each lesion, resulting in a 100% histopathologic yield from the 6 patients. The reason for our low yield (71.4%) may be due to the fact that our study is a retrospective study conducted at multiple hospitals and only one to three biopsies were taken from each lesion. Obtaining multiple biopsy specimens might increase the histopathologic yield. However, looking at our study from another point of view, only duodenal biopsies were able to establish a diagnosis when the stool analysis was negative in 6 (24%) patients, which lead to the avoidance of a fatal outcome.

In conclusion, *S. stercoralis* hyperinfection can rapidly become fatal, so early diagnosis and treatment is very important. Although diagnosis is usually made by stool analysis, our results clearly demonstrate that endoscopic observation and biopsies, in addition to gastroduodenal drainage analysis, are important tools for diagnosing strongyloidiasis. We also emphasize that infection with *S. stercoralis* and HTLV-1 should be ruled out before immunosuppressive therapy is administered for patients living in or coming from endemic regions.

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COMMENTS

Background

Strongyloides stercoralis (*S. stercoralis*) is an intestinal nematode that infects about 100 million people worldwide. As *S. stercoralis* colonizes in the duodenum, endoscopic evaluation has been recognized as an important tool for diagnosing strongyloidiasis. Although there have been several case reports demonstrating endoscopic findings of strongyloidiasis, the relationship of endoscopic markers to clinical and histopathological findings have not been intensively studied.

Research frontiers

There is an increasing body of epidemiological evidence regarding the association between *S. stercoralis* infection and HTLV-1 infection. Studies of molecular mechanism of this association have become one of the hot spots at present. For the diagnostic purpose, detection of *S. stercoralis* in clinical samples has been improved by the agar plate culture method which was invented recently.

Related publications

Nakada *et al*[21] clearly disclosed the first evidence of the association between *S. stercoralis* infection and HTLV-1infection. Hirata *et al*[24] conducted a large

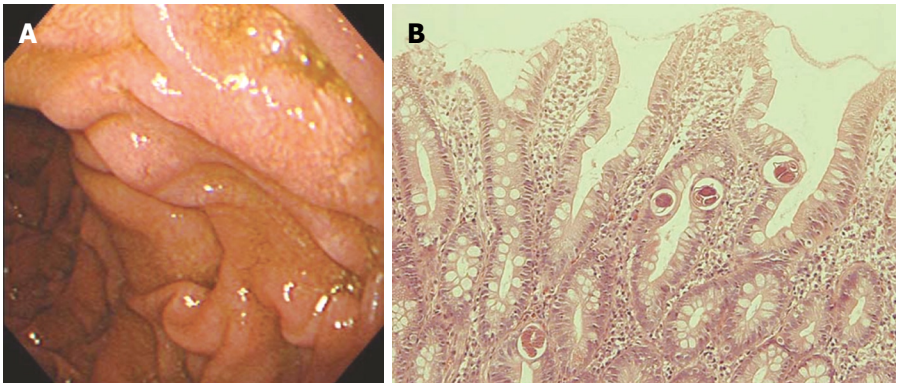

Figure 3 Representative endoscopic image and HE staining of duodenal biopsy. **A**: EGD showing white villi and edematous mucosa in the second part of duodenal (Case 11); **B**: Biopsy specimen from the mucosa showing numerous larvae with villous atrophy and mild inflammatory cell infiltration (HE, × 200).

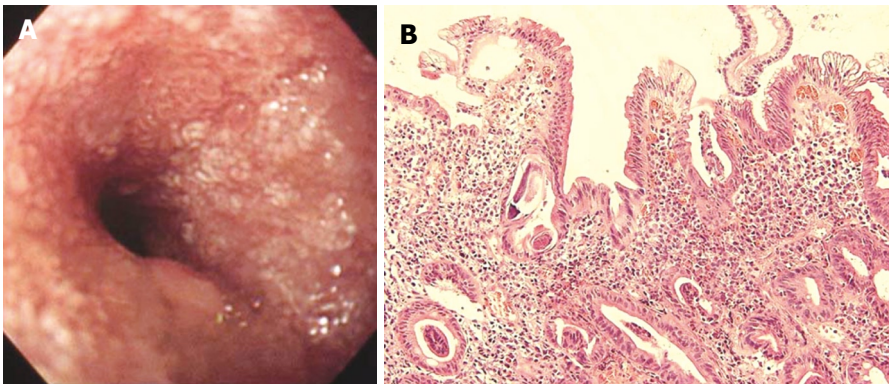

Figure 4 Endoscopic image and HE staining of duodenal biopsy. **A**: EGD showing white villi and stenosis in the second part of duodenal (Case 16); **B**: Biopsy specimen from the mucosa showing numerous larvae with severe villous atrophy and moderate inflammatory cell infiltration (HE, × 200).

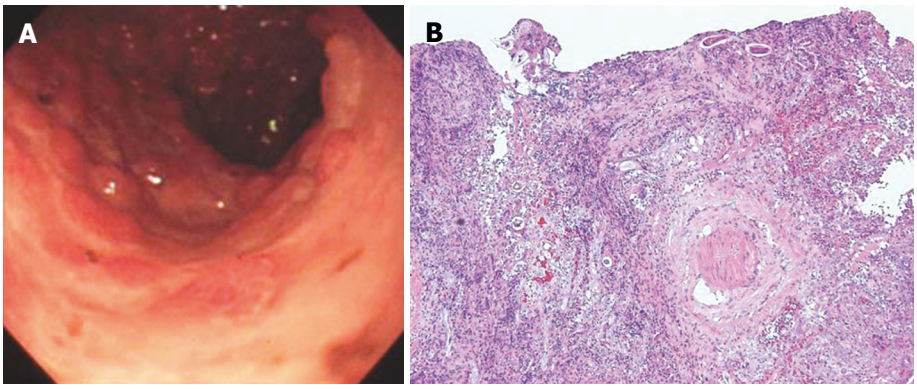

Figure 5 Endoscopic findings and HE staining of duodenal biopsy. **A**: EGD showing large ulcers and pseudopolyps in the second part of duodenal (Case 15); **B**: Biopsy specimen from the margin of the ulcer showing formation of granulation tissue and complete destruction of the villi. Numerous larvae are observed within the granulation and lymph vessels (HE, × 100).

Table 3 Reported endoscopic findings of the duodenum with strongyloidiasis in literature

Authors	Year	No. of cases	Immunosuppressive state	Endoscopic findings of the duodenum
Brasitus *et al*[3]	1980	1	None	Brisk bleeding, deformed bulb
Milder *et al*[4]	1981	2	ND	Enlarged folds
Bone *et al*[5]	1982	1	ND	Deformed cap, obliterated second part
Bhatt *et al*[6]	1990	1	None	Mild erythema
Chen *et al*[7]	1994	1	Corticosteroids	Flattened folds, swelling mucosa, tiny ulcer
Choudhry *et al*[8]	1995	3	DM, none	Multiple serpiginous lesions, duodenal nodule
Hizawa *et al*[9]	1996	1	HTLV-1 and corticosteroids	Edema, tiny white spots
Friedenberg *et al*[10]	1999	1	HTLV-1	Severe stenosis
Overstreet *et al*[11]	2003	1	HIV	White punctate dotting mucosa
Asano *et al*[12]	2004	1	HTLV-1	Fine granule, coarse mucosa, disappeared folds
Thompson *et al*[13]	2004	6	Corticosteroids, DM, HIV, none	Edema, brown discoloration, erythematous spots, subepithelial hemorrhage, megaduodenum
Seet *et al*[14]	2005	1	Anti-myeloma drugs	Erythematous and granular mucosa
Karmo *et al*[15]	2006	1	Corticosteroids	Normal
Ghoshal *et al*[16]	2006	1	Corticosteroids	Multiple nodules
Werneck-Silva *et al*[17]	2006	4	ND	Erythema, erosion
Csermely *et al*[18]	2006	1	Anti-myeloma drugs	Necrotic ulcerations
Suarez and Sanchez[19]	2006	11	ND	Swollen folds of nodular aspect

ND: Not determined.

scale epidemiological study which strengthened this association and showed the impairment of host immune response against *S. stercoralis* by HTLV-1 infection.

Innovations and breakthroughs

This study clarified the strong association between *S. stercoralis* hyperinfection and HTLV-1 infection. Moreover, presence of white villi can be a good endoscopic marker for the duodenal strongyloidiasis. Endoscopic biopsy helped early diagnosis of strongyloidiasis.

Applications

Early endoscopic diagnosis of strongyloidiasis can have a marked impact on disease outcome. Co-infection with *S. stercoralis* and HTLV-1 should be ruled out to prevent hyperinfection before immunosuppressive therapy (e.g., corticosteroids) is administered for patients living in or coming from endemic regions.

Terminology

Hyperinfection is a syndrome of accelerated larval autoinfection which results from immunosuppression. Disseminated strongyloidiasis is the migration of larvae to organs beyond the range of the autoinfective cycle and is often complicated by Gram-negative sepsis which results in high mortality rates.

Peer review

This is a well conducted study clarifying the strong association between *S. stercoralis* hyperinfection and HTLV-1 infection.

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