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PATHOLOGY OF FATAL STRONGYLOIDIASIS

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SUMMARY

In 13 fatal human cases of Strongyloidiasis migrating larvae in several tissues and a dense parasitism of the duodenal and jejunal mucosal crypts by adult females, ova and larvae of *Strongyloides stercoralis* were seen.

Migrating intact larvae evoked no tissue reaction, while desintegrating larvae elicited slight inflammatory changes of apparently no functional significance. In four cases ulcerative colitis was produced by the penetration of numerous parasitic larvae through the mucosa. Lungs showed intra-alveolar hemorrhage, which in some cases was so marked as to grossly simulate pulmonary infarcts. Such hemorrhage occurred in the presence of only a few larvae in the lung sections.

The findings in the present series favor the ideia that the establishment of an internal auto-infecting cycle by strongyloides larvae, resulting in intense intestinal parasitism and secondary bacterial invasion, is of prime importance in the genesis of severe or fatal strongyloidiasis.

INTRODUCTION

Most studies on the pathology of strongyloidiasis have been based on single cases [2, 3, 11, 16, 17, 18], or, in a few instances, on short series of cases [4, 5, 15]. DE PAOLA'S recent study [7] of 10 autopsied cases represents an exception. Although, as a result of all these investigations, and also of experimental studies [10], the pathology of the disease is now well established in its main aspects, the study of larger series of cases is still of interest. It permits a better appreciation of pathology and pathogenesis, an evaluation of the relative frequency of lesions and is an indication that the severest forms of the disease are not a rarity. The frequency of fatal strongyloidiasis in Brasil, together with the high incidence of this helminthiasis [5, 6, 14] has lately aroused a great interest among Brazilian investigators [4-7, 14]. These facts stimulated the present report, which is a morphological study of 13 fatal cases of strongyloidiasis. It includes observations on the reactions around migrating larvae in several organs and the demonstration of severe damages in the upper intestine, colon and lungs due to the parasitism. An attempt is made to consider these lesions in relation to some fundamental aspects of the pathogenesis of strongyloidiasis.

MATERIALS AND METHODS

Clinical records and autopsy protocols from 13 fatal cases of strongyloidiasis were examined. In all cases severe Strongyloides infection was demonstrated microscopically, and in all of them the main clinical symptomatology and usually the cause of death could be directly ascribed to the parasitism.

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TABLE I

General clinical data on 13 fatal cases of strongyloidiasis

No.	Age	Sex	Color	Duration of symptoms
1	49	M	W	3 years
2	56	F	N	8 months
3	16	F	N	6 years
4	11	M	N	15 days
5	27	M	N	3 months
6	44	M	N	40 days
7	43	F	N	15 years
8	25	F	N	2 years
9	19	M	N	?
10	4	M	N	?
11	4	M	N	5 months
12	19	M	N	3 months
13	15	M	N	1 year

TABLE II

Main clinical findings in 13 fatal cases of strongyloidiasis

Symptoms	No. of cases	%
Diarrhea	13	100.0
Vomiting	11	84.5
Abdominal pain	8	61.5
Peripheral edema	6	46.2
Cough with bloody sputum	4	30.7

TABLE III

Gross intestinal lesions in 13 fatal cases of strongyloidiasis

Lesions	No. of cases with lesions in		
	Small intestine	Colon	Rectum
Mucosal edema and congestion	13	8	4
Ulcerations	6	4 *	2
Disappearance of mucosal folds ..	5	—	—
Punctate hemmorrhage	—	2	—
Pseudo melanosis .	—	2	1

* One case also had associated amebic lesions.

A complete autopsy was performed in every case. The material for histological examination was fixed in 10% formalin, embedded in paraffin and the sections stained by the following techniques: hematoxylin-eosin, PAS' method, Gomori's trichrome stain, Weigert-Van Gieson technich for collagen and elastic fibers, toluidin blue for metachromasia and alcian blue for acid mucopolyssacharide.

RESULTS

Summary of clinical data — The main clinical findings are tabulated in Tables I and II. Severe diarrhea, sometimes with bloody discharge, was the dominant feature in every case. In consequence, symptoms and signs of dehydration and malnutrition were conspicuous. In 4 cases reference was made to the presence of cough with bloody sputum. Stool examination performed in 9 cases showed Strongyloides larvae in 8, and also eggs of *Ancylostoma sp.* (3 cases), *A. lumbricoides* (3 cases), *S. mansoni* (2 cases) and *T. trichiurus* (5 cases). Serum protein level was low in every case (Maximum for albumin 3.1; average 1.5; and minimum 0.3 g%. The corresponding values for globulin were: 3.1; 2.5; and 1.5 g%). Edema of the lower extremities was present in 6 patients, some of them also showing palpebral edema. Three patients died with clear-cut signs of acute dehydration, while the remaining presented a picture of peripheral shock shortly before death.

Gross autopsy findings — Emaciation, or even extreme degrees of cachexia, was found in every case. A 4 year old boy showed distrofic lesions of the skin and hair, a diffuse fatty liver and pancreatic atrophy and could be considered as a case Kwashiorkor. Thrombophlebitis of the right popliteal and tibial veins and pulmonary embolism wese demonstrated in Case 2. Case 5 presented thrombophlebitis of the left jugular, axilar, brachial and right femoral veins. The peritoneal cavity contained 30 to 700 ml of a clear yellowish transudate in five cases. The peritoneal lining was always glistening, smooth and no adhesions were observed between the intestinal loops. The small intestine was distended, sometimes considerably so, and was edematous and congested. The mesenteric lymph nodes were

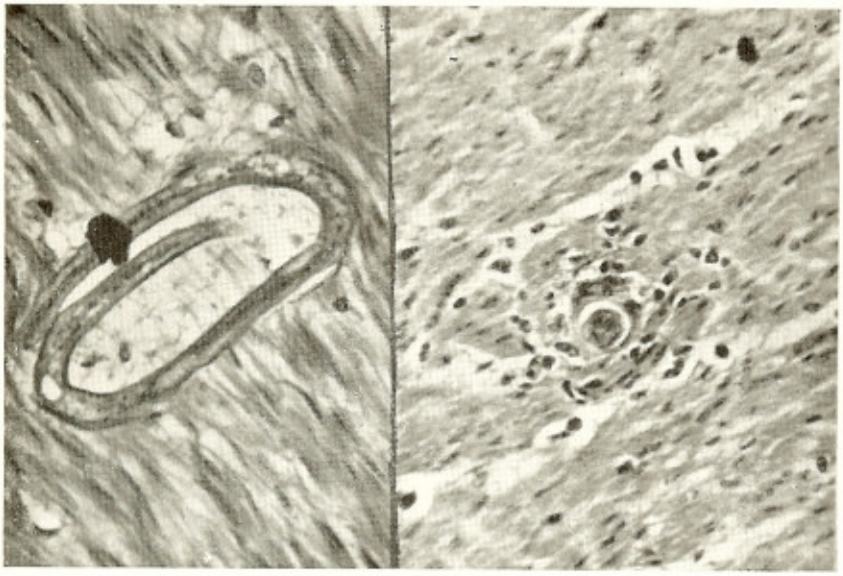

Fig. 1 — *Left*: intact strongyloides larva in the muscular coat of the colon, showing no cellular reaction around it (H. E. 150 ×; *Right*: Slight cellular reaction around desintegrating larva present in the muscular wall of the colon (H. E. 100 ×).

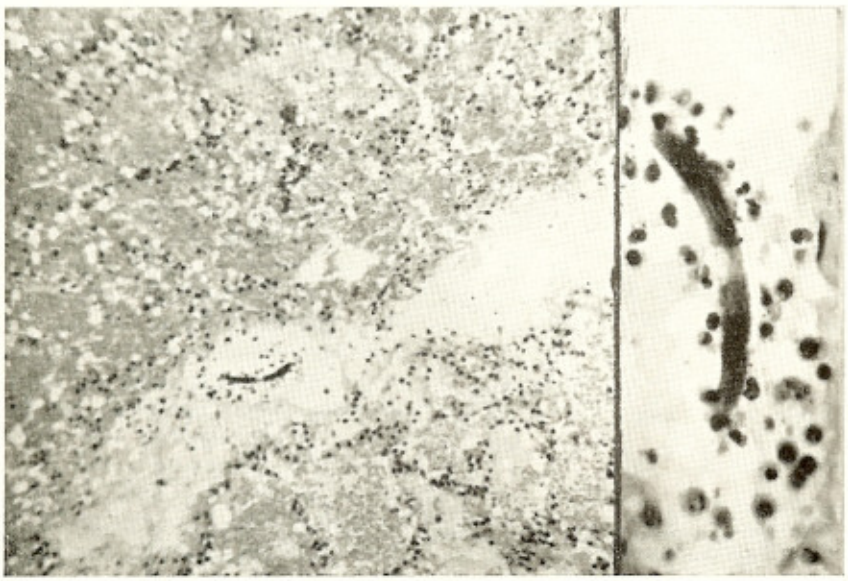

Fig. 2 — *Left*: Section of lung showing interstitial edema and dense intra-alveolar hemorrhage (H. E. 100 ×); *Right*: Strongyloides larva present in interstitial tissue of the lung is show in high magnification (H. E. 430 ×).

slightly enlarged due to congestion and edema. In one case these nodes were stained green by medication introduced into the intestine (Dithiazanine). Case 5 presented caseous tuberculosis of the mesenteric and mediastinal lymph nodes. Gross changes presented in the intestinal mucosa are tabulated in Table III. In seven cases the mucosa of the small intestine showed minimal changes, represented by edema, congestion and disappearance of the circular folds. The remaining cases showed multiple ulcerations in the duodenum and proximal jejunum. These lesions were small (2 mm up to 1 cm. in diameter), round, confluent, shallow, with irregular and slightly elevated edges and a smooth or finely granular floor. The mucosa sometimes presented a mottled pattern. Similar ulcerative lesions were also present in the colon in four cases.

The lungs showed a variable degree of congestion, edema, focal areas of bronchopneumonia and fibrous adhesions between the pleuras. Extensive areas of hemorrhage, with no particular distribution within the lungs were seen in many cases. These hemorrhagic areas were sometimes so dense as to simulate pulmonary infarcts. Pulmonary tuberculosis was present in four cases. In two of these there were small focal areas of caseous tuberculosis in the lung and mediastinal nodes. There was one instance of miliary tuberculosis and one extensive tuberculous pleuritis. Gross changes found in other organs were not remarkable, except for the presence of diffuse fatty metamorphosis of the liver in 3 cases.

Microscopic findings — Small intestine: Adult females of *S. stercoralis* together with their larvae and embryonated ova were found lodged in large numbers in the crypts of the duodenal and upper jejunal mucosa. Near the parasites there was dilatation of the crypts and atrophy of the mucosal cells. No increase in the number of mucous producing cells was observed. No inflammatory reaction was detected around the parasites in the mucosa. The connective tissue of the lamina propria and submucosa disclosed a slight to moderate diffuse infiltration by macrophages, lymphocytes, and plasma cells. Neutrophilic polymorphonuclear leucocytes were present in small numbers and occasionally formed micro-abcesses in the mucosa. Eosinophils were either rare or absent. In the presence ol ulceration, which rarely reached the submucosa, the inflammatory reaction became accentuated and extended as far as to dissociate the fibers of the muscular layer. Parasitic elements could be detected at the base of the ulceration, but only a few larvae were present deep in the intestinal wall. The submucosa was enlarged by edema, which sometimes took a homogeneous deeply eosinophilic appearance. Alcian blue stained lightly this edematous tissue and the toluidin blue stain failed to demonstrate metachromasia. Fibrosis of the submucosa was always slight in the cases studied. No evidence of lymphatic ectasia or blood vessel inflammatory involvement could be seen. Deformation of intestinal villi due to edema and cellular infiltration sometimes resulted in a "sprue-like" appearance of the jejunal mucosa.

Reaction around migrating larvae — Migrating larvae were observed in all intestinal hayers, a few in the duodenum, jejunum and ileum, and many in the colon, specially in the submucosa and muscular. The stomach was also envolved and in one instance a larvae was found going through the esophageal mucosa. Larvae were also observed in the lungs, mesenteric lymph nodes, liver and pancreas, but no especial effort was made to search for them in the several organs. They were found within lymphatics, blood vessels and in the tissue spaces. Intact larvae evoked no tissue reaction at all (Fig. 1a). Desintegrating larvae were surounded by a few macrophages, plasma cells and occasional giant cells of foreign body type (Fig. 1b). The reaction was always small, well defined and quite uniform regardless of the organ affected. No necrosis was ever seen. Diffuse non-specific acute and chronic inflammation was seen in the vicinity of migrating larvae in the intestinal chorion and submucosa and sometimes in the lungs, but not elsewhere.

Colon — Occasionally, adult worms, larvae and ova were found in the Lieberkuhn glands of the large intestine in the absence of cellular reaction. Ulcerative lesions similar to those found in the small intestine, were observed in four cases, together with a great number of Strongyloides larvae. In two cases the ulcerations were also found in

the rectum. In one case presenting ulcerations going deep into the submucosa, several tissue forms of *E. histolytica* were also seen. The Auerback plexus exhibited no changes.

Lungs — Alveolar hemorrhage was seen in practically every case, being particularly severe in six. The alveolar space was free of hemorrhage. (Fig. 2). The severity of the alveolar hemorrhage was not related to the number of parasitic larvae present in the multiple sections examined. No thrombi, necrosis or inflammation were seen involving the blood vessels. No destruction or thickening of alveolar wall was observed. The process was apparently independent of bronchopneumonia or caseous tuberculosis present in some cases.

Changes observed in other organs were not considered of importance for the present communication.

COMMENTS

A striking feature in the microscopic picture of the cases here described was the monotonous similarity of the reaction around desintegrating larvae in different organs and in different individuals. The reaction was a minimal one and consisted of an accumulation of a few macrophages, plasma cells and one or two giant cells. No individual variation indicative of a possible allergic or hypersensitive factor was recorded. Necrosis, intense eosinophilic infiltration, exsudative changes, were absent. Marked inflammatory lesions in the intestinal mucosa and lungs were due to secondary bacterial invasion, as had been claimed for a long time. FAUST [8] said that *S. stercoralis* is as yet young in the field of parasitism, still presenting a free living cycle. Adaptation to man seems to be quite incomplete. The ability of this worm to produce severe disease in man apparently depends on the accumulation of large numbers of specimens in the intestinal mucosa, capable of causing multiple small ulcerations and permiting secondary bacterial invasion. The presence in our cases of numerous penetrating larvae in the intestinal wall, specially in the colon, is in agreement with the concept of the importance of internal auto-infection in the pathogenesis of the severest form of the disease [9]. This mechanism explains the severe cases of strongyloidiasis appearing in individuals many years after they moved out from endemic areas [13]. What causes the larvae to become infective while in the intestinal lumen is yet unknown, but this is the key problem for getting treatment and profilaxis of strongyloidiasis on a sound rational basis.

DE PAOLA [7] claims a fundamental role for intestinal lymphatic obstruction in the pathogenesis of strongyloidiasis. The migration and destruction of larvae within the lymphatics of intestinal submucosa would result in lymphoedema and terminal fibrosis of the gut. The presence of diffuse fibrosis of the upper intestine [6, 7, 17] and the development of lesions comparable with regional enteritis [12] in some cases of advanced strongyloidiasis is in keeping with the ideia of lymphatic obstruction. However, our findings were not consistent with a prominent participation of lymphatic obstruction by strongyloides larvae in the genesis of intestinal lesions. The latter were rare in the duodenal and jejunal submucosa and numerous in the colon while the distribution of edema and fibrosis showed a reverse situation.

Changes in the colon due to strongyloidiasis have been mentioned by several authors [4, 7, 12] but they need to be re-emphasised. One patient of our series was thought to have idiopathic ulcerative colitis. Anatomically, there were multiple ulcerations extending from the cecum to the rectum, while the changes in the small intestine were minimal and no ulceration was seen. Differently of what occurs in the small intestine, the colon lesions are due to the penetration of large number of larvae rather than to the presence of adult worms and their derivates in the Lieberkhun crypts. In both cases secondary bacterial invasion is of course of paramount importance. The lesions differ from those due to *E. histoytica*, because the former are superficial, usually not going beyond the muscularis and the worms show no tendency to penetrate underneath the border of the ulceration. In one case, lesions caused both by *S. stercoralis* and *E. histolytica* were present in the same section.

It has been said that pulmonary changes due to intestinal parasites should be suspe-

cted whenever dyspnea, cough, or hemoptysis occur in an individual who complains of abdominal pain, diarrhea, or other digestive tract difficulties [1]. Changes in the lungs were the rule in the cases studied. Besides the presence of patchy areas of bronchopneumonia and tuberculosis in some cases, the main finding was a diffuse, sometimes marked, intra-alveolar hemorrhage. Clinically, four of the patients presented cough with bloody sputum and none of those had tuberculosis. In six cases the alveolar hemorrhage was quite intense and entirely out of proportion to the number of parasitic larvae found in multiple sections. Factors other than a mere mechanical on,e might be involved. A local defect in blood coagulation, capillary fragility or an isolated organ hypersensitivity of the Sanarelli's type are some of the possibilities.

SUMÁRIO

Patologia da estrongiloidose fatal

Em 13 casos fatais, foram observadas alterações em tôrno de larvas migrantes em vários órgãos e intenso parasitismo das mucosas duodenal e jejunal, e às vêzes também do colon, pelas fêmeas adultas, ovos e larvas do *S. stercoralis*.

As larvas intactas não provocaram alterações nos tecidos, enquanto que aquelas em desintegração eram circundadas por discreta reação granulomatosa, com alguns histiócitos, plasmócitos e raras células gigantes. Em 4 casos, o grande número de larvas causou extenso processo de colite ulcerativa do grosso intestino. Em todos os casos havia hemorragias pulmonares, intra-alveolares, sendo em alguns tão intensas que simulavam enfartos. Tais hemorragias não apresentavam relação direta com o número de larvas presentes nas secções, sendo possível que outros fatôres tenham influído na sua patogenia.

Êstes achados reforçam o conceito de que o estabelecimento de um ciclo de auto-infecção interna é elemento fundamental na patogenia da estrongiloidose grave, a qual se faz em função da intensidade do parasitismo intestinau seguido de infecção bacteriana secundária.

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