J. Rakuno Gakuen Univ., **33** (1) : 139～150 (2008)

Gastroenteropathy in rodents with hepatic *Taenia taeniaeformis* larvae infection: mechanism of pathogenesis

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(Accepted 24 July 2008)

Abstract

Parasites generally produce histopathological changes in organs or tissues of hosts where they are located. Hepatic *Taenia taeniaeformis* larvae infection in rodents, however, has been reported to induce gastric and intestinal hyperplasia despite the fact that the parasite is located remotely. This unique phenomenon suggested that in a host-parasite relationship, unforeseen pathological complications may occur in the infected host. Several mechanisms were hypothesized to influence gastroenteropathy in rodents during hepatic *T. taeniaeformis* larvae infections. Hypergastrinemia and immunosuppression were suggested to contribute to the development of lesions but recent studies showed inconsistencies of their association. More prominent among proposed geneses indicated factors from the larvae might cause this phenomenon. Excretory-secretory products of *T. taeniaeformis* larvae were proven to induce the hyperplastic lesions in the gastric mucosa of immunodeficient mice. Previous studies hinted that the larvae products were absorbed into the host's body and carried by the blood into the gastroenteric mucosa. Immunohistochemical studies have also supported the premise that the products were associated with hyperplastic lesions found from gastric to colonic mucosa of infected rodents. This review highlights the pathogenesis of gastroenteropathy during hepatic *T. taeniaeformis* larvae infection in rodents.

Introduction

In 1926, Johanes Fibiger won the only Nobel Prize for helminthology in inducing gastric cancer in rats by feeding them cockroaches infected with *Spiroptera neoplastica* (later renamed *Gongylonema neoplastica*) larvae. Although it was later criticized as not being true cancers, but merely worm-induced hyperplasia associated with vitamin A deficiency[40], it showed how parasites can produce lesions in their hosts. Generally, parasites produce histopathological changes in organs or tissues of hosts where they are located. In the case of parasites in liver, hepatic tissues and related organs suffer from either mechanical or immunological reactions. The pathologies are evoked by either the parasites or as hosts' responses against the invading organism. Likewise, in gastrointestinal parasitism, abnormalities are observed in specific sites of the digestive tract where the parasites are located. There are records, however, of parasite-free regions showing histological changes as a form of compensatory mechanism to incapacitated parasitized regions[20].

Hepatic *Taenia taeniaeformis* larvae infection in rats has been known to induce gastric and intestinal hyperplasia despite the fact that the parasite is located remotely in the liver[1,4,11,25,29,30,36,48]. This unforeseen consequence of pathology remote from the site of infection is a unique phenomenon in the aspect of parasitism. A dynamic and rapidly developing area of research in host-parasite relationship studies is

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the identification of immunomodulatory molecules from parasites[14]. On the other hand, increasing evidences of parasites causing cancer in hosts have been documented[40].

This review will highlight the different theories involved to explain the pathogenesis of *T. taeniaeformis* induced gastroenteropathy and aims to build on a greater understanding of the mechanism in the development of lesions. We presumed that a clearer grasp of this unique pathogenesis will advance knowledge of host-parasite relationships. Nevertheless, gaps are still apparent and need to be investigated towards full comprehension of this phenomenon and similar gastroenteropathies.

Parasitism and pathologies

Parasitism is a relationship of two organisms of different species in which the smaller (the parasite) has the potential of harming the larger (the host), and the parasite relies on the host for nutrient and for a place to live[38]. On one hand, since the parasite is dependent on its host, it is to its own advantage not to destroy the host. Although there are many species of parasites that are harmless to their host, there are also many forms that produce pathological changes and could lead to severe ill health or death of the host[59]. In order for a successful adaptation of the parasite in its host, it may induce conditions favourable for its own development and metabolism. Such favourable conditions could involve in maintaining an adequate body size and food supply, inducing immunosuppression and analgesia in the host, and influencing the speed of development of the host[58]. These mechanisms substantiated that there are effecter molecules secreted or excreted by some parasites that could cause unforeseen circumstances in host-parasite relationships.

To survive for long periods in a disadvantageous and aggressive environment, helminth parasites secrete several soluble factors that might interact with host cells and interfere cell to cell communications processes, thus would contribute into pathologic processes[17]. One classic example is the plerocercoids of Spirometrid tapeworms synthesizing and releasing plerocercoid growth factor that is transported by the blood, interacts with growth hormone receptors and mimics many of the biological actions of growth hormone[45].

Helminths such as *Schistosoma haematobium* and *Opisthorchis viverrini*, have been proven to be definitely carcinogenic to humans. Mechanisms of helminth-induced cancer are reported to include chronic inflammation, modulation of the host immune system, inhibition of intracellular communication, disruption of proliferation-antiproliferation pathways, induction of genomic instability and stimulation of malignant stem cell progeny[40].

Taenia taeniaeformis infection and gastroenteropathy in rodents

Taenia taeniaeformis is a tapeworm inhabiting the small intestine of the definitive hosts: cats and other carnivores. Gravid segments of the tapeworm containing the infective eggs are excreted with the hosts' feces. Rats, mice, and other wild rodents are known intermediate hosts and are infected by ingestion of the tapeworm eggs. These rodents harbour the hepatic dwelling larval stage, *Strobilocercus fasciolaris*. When infected rodents are preyed upon by susceptible carnivores, the larvae develop into tapeworm stage in the small intestine of definitive hosts to continue the life cycle of the parasite.

Bullock and Curtis[7,8] first observed "hepatic sarcomata" in chronically infected rats that was reported to disseminate throughout the abdominal cavity. "Hyperthropic gastritis" was described that caused the increase of stomach size in heavily parasitized rats[9]. Blumberg and Gardner[5] further described morphologically the increase of stomach size in heavily and chronically infected rats as more than double compared to the normal rat stomach.

After more than half a century, Cook and Williams[11] revisited the pathological changes in the stomach and small intestine by oral infection of rats with *T. taeniaeformis* eggs. This was followed by a parabiosis experiment that led to a hypothesis on the involvement of a chemical mediator or factors released by the larvae[12].

Investigation of gastroenteropathy in chronically infected rats up to 12 months of infection was made and found the lesions to intensify rather than subside[4]. An *in vitro* experiment on the effect of larval products on host gastric cells supported the hypothesis that factors from larvae are involved[49]. The same laboratory had demonstrated that larvae excretory-secretory products were located in the cytoplasm of hyperplastic cells by immunoperoxidase staining[50]. Further investigation on larval products was made by intraperitoneal implantation of larvae into rats inducing gastropathy[26].

It was also reported that the neutral mucous cell was the major type of hyperplastic mucous cells observed[48]. Electron microscopic studies were done in hyperplastic cells and suggested undifferentiated cells as the primary proliferating cells[25].

The effect of gastrin and gastric alkalinity was also indicated as a secondary factor in the development of lesions. It was confirmed also that there is a concomitant occurrence of gastric hyperplasia, hypergastrinemia, and intragastric alkalinity[1].

Immune down regulation during the course of infection facilitating the hyperplastic stimulus and earlier occurrence of gastropathy in immune deficient rats was suggested[2]. Using severe combined immune-deficient (SCID) mouse as animal model, oral, intraperitoneal and subcutaneous inoculation of *T. taeniaeformis* eggs or *in vitro*-hatched oncospheres and larvae implantation resulted in various degrees of gastropathies[27].

Gastroenteropathy is described grossly as significant enlargement of the stomach and small intestine. Excessive mucus productions with focal lesions of white plaques or nodules were observed in gastric mucosa. The most common visible lesion observed was of diffuse nodular mucosal thickening of the gastric inner wall. The mucosa of the small intestine was also thickened particularly in the duodenum and proximal jejunum with mucoid intestinal contents. Recent study observed colonic mucosa appearing edematous as well.

Microscopically, the gastric mucosal length was markedly increased and normal structure of gastric units composed of the pit, isthmus, neck and the base could not be identified. Mucosal hyperplasia is characterized by Periodic acid-Schiff reaction (PAS) and PAS-alcian blue (PAB) positive cells as responsible for multi-fold increases in height of gastric units. Konno et al.,[25] observed by electron microscopy that features of these cells were immature-like mucous cells. These cells were observed to be pit or neck mucous precursor cells occupying dilated gastric glands. Numerous cystic cavities were also found filled with PAB-positive mucus. Significant loss in the number of parietal and zymogenic cells in the gastric mucosa was observed[29]. Patchy infiltration of mononuclear cells and eosinophils were also seen[11].

Small intestinal changes comprised up to 2-fold increases in villus and crypt lengths but there was no significant changes observed in epithelial cell numbers. In chronic infection, distortion of normal architecture of the mucosa was observed due to the accumulation of mucus and subsequent dilation of the crypts. These dilatations contained a mixture of strongly PAS-positive mucus, sloughed epithelial cells and pyknotic nuclear fragments, which often become calcified. Intestinal mast cell and eosinophil counts were observed to have increased in number. Recent studies in rats also showed a 2-fold increase of mucosal cell number in the duodenum[29].

Present results showed mucosal length of colon increasing up to 3-4 folds with goblet cell number significantly greater than the control. Few cystic dilatations were found similar to the small intestines.

Pathogenesis of gastroenteropathy during hepatic *T. taeniaeformis* larvae infection

Taenia taeniaeformis *larvae excretory-secretory products*

Involvement of either chemical mediators or excretory-secretory products of *T. taeniaeformis* larvae had been suggested as the primary cause for inducing gastric hyperplasia in infected rats. Cook et al.,[11] first postulated that larvae derived

chemicals/factors transported by blood circulation are involved because an uninfected rat joined surgically to a heavily infected partner by parabiosis showed gastroenteropathy. Excretory-secretory products of larvae were reported to stimulate growth of host gastric cells *in vitro*[49], and were observed to be concentrated in specific areas of the cytoplasm of hyperplastic stomach epithelial cells[50]. This observation prompted Blaies and Williams[4] to attempt inducing gastric hyperplasia in rats by larval implantation of 40 larvae and intraperitoneal injection of TtLES (*T. taeniaeformis* larvae excretory-secretory) product into rats. Although the result was a failure, a follow up study increasing the number of larvae implanted (150-300) into the peritoneal cavity of rats induced gastric hyperplasia[26]. This finding suggested that the volume of excretory-secretory product played an important role.

Using severe compromised immune-deficient mouse proved that inoculation forms of parasites and routes of infection influenced larval development and affected initiation of gastric hyperplasia[27]. Inoculation of either parasite egg or oncospheres was preferably by oral route because it facilitated the infection into the organ of predilection (liver). Similarly, intraperitoneally inoculated *in vitro*-hatched oncospheres that were able to penetrate the liver of SCID mice also grew faster than those inhabiting the peritoneal cavity. Apparently, the development of larvae was faster in the liver than in other sites of infection.

The common denominator of all these factors —— the inoculation form of parasite and route of infection —— rests upon which produced the greater number of large sized larvae that resulted to gastroenteropathy. Induced gastric hyperplasia is suggested as being dependent on the number and size of larval cysts. The volume of excretory-secretory products apparently was relative to the size and number of larvae[26,48].

A significant correlation was observed between increase of stomach weight in infected rats and the number of hepatic larvae in rats at 12-20 weeks post-inoculation[48]. Increasing the number of implanted larvae into rats induced hyperplastic lesion. Inoculated SCID mice revealed that the degree of gastric hyperplasia was dependent on number and size of developed larvae[27]. This correlated to recent observations that *in-vitro* culture of 9-week old larvae produces lesser gram of protein per larvae than larger 12-week old larvae. Furthermore, daily injection of 1 mg protein/day resulted to gastric mucous pit cell hyperplasia and decrease in parietal cell number at 1 WPI while those injected with 0.5 mg protein /day did not show significant changes in gastric mucosa until 4 WPI[28]. These findings proved that volume of the TtLES product is an important factor in the development of gastric hyperplasia.

Hammerberg and Williams[16] reported that *T. taeniaeformis* larval *in vitro* products contained polysulfated glycosaminoglycan. These molecules have been detected on surfaces of various infectious organisms. Glycosaminoglycans were suggested as playing a role in the healing process of acetic acid ulcer in rat stomach[60]. Parasitic glycosaminoglycans were suggested to stimulate the growth of gastric epithelial cells[49].

Gastroenteropathy and immunity

Immunity was observed to be a factor that influences length of pre-patent period (period from inoculation until development of gastric hyperplasia). Eventual down regulation of host immune response during the course of infection presumably by larval proteinase inhibitor was suggested[2]. Immune response of host once inhibited may facilitate the action of TtLES product. Infected athymic nude rats developed gastric hyperplasia earlier than euthymic rats that implicated T cell mediated response as involved. Immunodeficient mice lacking T cell responses also developed gastric hyperplasia sooner than immunocompetent ones. On the other hand, T cell dependent cell mediated responses were noted in resistance to *T. taeniaeformis* infection as early as 5 days post infection[21]. Collating these results would indicate that T cell responses affect establishment and might inhibit growth of larvae, to which the volume of TtLES product was dependent. T cell immune response therefore is suggested to affect gastric hyperplasia indirectly by

its action on development of larvae.

A study had suggested the possibility that locally produced inflammatory and T cell derived cytokines could facilitate hyperplastic changes[62]. To the contrary, development of gastropathy in *T. taeniaeformis* infection was observed earlier in athymic nude rats in the absence of T cell-mediated responses over immunocompetent rats[2]. Later occurrence of gastropathy in immune competent rats might have suggested the role of T cell immune response in resistance to *T. taeniaeformis* infection[21], that may have an effect on the establishment and growth of larvae. *T. taeniaeformis* induced gastric hyperplasia in SCID mice lacking any T cell-mediated responses[6] further supported these observations. Larval cyst size and number are found to be very important factors in inducing the hyperplastic lesions as revealed by these results.

Hypergastrinemia and increase of intragastric pH

The implication of gastrin in pathogenesis of gastric hyperplasia was suspected since this hormone exerts trophic effects on gastrointestinal tissues[63]. Serum gastrin concentration in rats infected with larval *T. taeniaeformis* was remarkably reaching up to 100-fold increase[12]. However, the same authors reported that antrectomized rats developed also gastric hyperplasia without elevation of serum gastrin levels. Abella et al.,[1] noted that there was simultaneous and abrupt occurrence of gastric hyperplasia, hypergastrinemia, and rise in intragastric pH in infected rats without prior alterations on these parameters. Further observations in chronic gastric hyperplasia for 1 year or more revealed that gastrin levels returned to normal level whereas the stomach was enormously enlarged. These findings suggested that occurrence of hypergastrinemia is secondary to gastric hyperplasia. It was also suggested that increase secretion of mucus by mucous cells leads to the rise of intragastric pH that resulted to hypergastrinemia[26].

On the other hand, loss of parietal cells had been consistently observed in hyperplastic mucosa. Loss of functional numbers of parietal cells was suggested to be due to preferential differentiation of stem cells to mucus-producing cells and pressure atrophy resulting from uncontrolled growth of surrounding cells[1]. SCID mice intraperitoneally inoculated with *in vitro*-hatched oncospheres were observed to have noticeable decrease in parietal cell number along with minimal increase in immature and mucous pit cell number at 2 WPI. Taking into account this result, it is conceivable that signs of parietal ablation could have occurred earlier than the concomitant onset of gastric mucosal hyperplasia, rise of intragastric pH and hypergastrinemia.

Parietal and zymogenic cells loss

Parietal cell loss was mentioned as probable cause in rise of intragastric pH and hypergastrinemia. Parietal cell loss was observed to be associated with the degree of mucosal cell hyperplasia. Significant loss of parietal cells in various degree of hyperplasia in SCID mice models corroborated with reports associating parietal cell loss with the development of characteristic changes of mucosal cell hyperplasia[25]. The mechanism of the loss of parietal cells in this phenomenon is unknown.

Extensive studies disclosed that nematode parasites inhabiting the stomach of mammalian animals have the ability to inhibit acid secretion causing increases in gastrin secretion[57]. Acid is generated in parietal cells in fundic region by proton pump. Abomasal nematodes may cause dysfunction or loss of parietal cells by blocking the proton pump or interfere with the complex pysiological regulation of the parietal cells[53]. Dysfunction and loss of parietal cells decreases acid secretion and cause the increase of pH in stomach. Removal of acid feedback in turn would cause hypergastrinemia in parasitized animals[31]. However, no concrete evidence yet can be shown that indeed parietal cell loss occurred prior to the rise of intragastric pH in *T. taeniaeformis*-induced gastric hyperplasia.

Reduction in the number of parietal cells during gastric hyperplasia in sheep transplanted with

adult and larval *Ostertagia circumcincta* was postulated to be due to the parasites releasing chemical/s with possible detrimental effects on parietal cell function and survival[54]. A sequential study in sheep transplanted with 20,000 adult *O. circumcincta* described features in parietal cells suggestive of necrosis[55], the normal process of death in parietal cells[27]. A nematode-mediated parietal cell dysfunction was reported in sheep infected with *O. leptospicularis* infective larvae[19] and was purported by a similar claim in an observation of *O. ostertagi* infection in calves that resulted in the loss of acid-secreting parietal cells[15]. An indirect suppression of parietal cells by inhibiting secretory activity of enterochromaffine-like (ECL) cells was induced by *Haemonchus contortus* ES product[18]. Both excretory-secretory products of *O. circumcincta* and *H. contortus* have been implicated in the inhibition of gastric acid secretion and vacuolation, and the loss of parietal cells associated with abomasal parasitism[41,47]. Simpson[57] suggested that parietal cell dysfunction was the key event that leads to loss of mature zymogenic cells and mucous cell hyperplasia in abomasal nematodosis. Nomura et al.,[43] established that parietal cells secrete a number of growth factors that influence the differentiation of other gastric lineages. The accompanying loss of zymogenic cells was likely a consequence of the interruption of the normal development pathway in the gastric mucosa that followed after destruction of parietal cells[39]. Parietal cells were observed to play a central role in the regulation of mucosal proliferation during gastric inflammations[3].

Apparent loss of parietal cells even before mucosal hyperplasia developed in SCID mice at 2 weeks post infection might be related with the reports in genetically engineered ablation of parietal cells that resulted in hyperplastic gastropathy[10,33]. Parietal cells are suggested to be able to influence proliferation of stem cells and modulate the terminal differentiation programs of mucous and zymogenic cells[10]. Blocking in the maturation of parietal cells was reported also to inhibit the terminal differentiation of zymogenic cell[33]. It was suggested that members of the parietal cell lineage are required for instructive interaction that affects differentiation of the zymogenic cell lineage at later stages of morphogenesis[23]. A form of compensatory enhancement of progenitor production involved due to the depletion of two major components of the gastric unit[33]. Pluripotential stem cells responded through increase mitotic activity continually accumulating cells that never differentiate into parietal and zymogenic cells.

Gastroenteropathy and growth factors

Transforming growth factor-alpha (TGF-α) is an important regulator of the proliferation, differentiation and physiological activity of gastric epithelial cells[32]. It has physiological functions similar to epidermal growth factor (EGF) and shares a receptor with it. Transgenic mice overexpressing TGF-α displayed mucous cell hyperplasia and diminution of parietal and zymogenic cells[56] similar to the *T. taeniaeformis* induced gastric hyperplasia. How parasites could alter production of growth hormone is still unknown. We have presumed in a previous report that ES products might contain cytotoxic molecules probably causing injury to the gastric mucosa[30]. This supposition was made in the light of the pathologic responses similar to other forms of gastric injury. Mucosal proliferation was observed following aspirin injury in rat stomach[44] and acute injury from hypertonic saline-induced denudation of gastric mucosa elicited a rapid upregulation of pathways leading to production of pit mucous cells[37]. Taken into consideration that excretory-secretory products can cause parietal cell loss and mucosal damage, both these events upregulate TGF-αexpression and promote foveolar hyperplasia and may further inhibit parietal cells[57]. In acute gastric injury, expression of TGF-αmRNA and protein in mucosa was reportedly increased[46]. In creased gastrodoudenal concentration of TGF-$\alpha$was also observed in aspirin induced gastric mucosal damage[51]. TGF-αtransgenic mice demonstrated severe mucous cell hyperplasia, glandular cystic dilatation, increased gastric neutral mucin staining and achlorhydia, the failure to secrete detect-

able gastric acid[13,61], which were characteristic of the *T. taeniaeformis* induced gastropathy. Furthermore, chronic TGF-α overexpression was described to disrupt the normal program of gastric epithelial cell differentiation[56]. Histologically, pit cells and isthmal precursor cells were greatly expanded while parietal and zymogenic cells were depleted. Moreover, mucous neck cells, precursors of zymogenic cells were found to be increased in transgenic mice and occupied the position taken by zymogenic cells in base region. These features were supportive for a case of TGF-α being involved with the anomaly described in this study.

Extracellular factors capable of receptor-mediated signal transduction were believed to play a prominent role in the complex regulation of stomach function, including cellular growth and differentiation[34]. These include epidermal growth factor (EGF) family of which TGF-α is a member[52]. *H. pylori* infection was reported to upregulate expression of amphiregulin and heparin-binding EGF-like growth factor at the mRNA and protein levels which was suggested to stimulate epithelial cell proliferation[64]. TGF-α and EGF immunoreactivity, however, was less observed in *T. taeniaeformis* infected rats showing gastric mucosal hyperplasia suggesting a pathogenesis independent from these growth factors[24]. Konno[24] assessed the involvement of this growth factor by EGF/TGF-α immunostaining the submandibular glands largely secreting EGF. Results showed that gastric hyperplasia still developed while there were no EGF/TGF-α positive cells stained within the hyperplastic mucosa. Development of mucosal hyperplasia even with the lack or absence of these growth factors supposedly involved in such lesions could evoked a presumption that TtLES product might contain molecules/proteins which can act similarly as EGF/TGF-α do. Plerocercoids of Spirometrid tapeworms synthesize and release plerocercoid growth factor that is transported by the blood, interacts with growth hormone receptors and mimics many of the biological actions of growth hormone[20].

Enteropathy, goblet and mucosal mast cell number increase

Enteropathy was also observed in *T. taeniaeformis* infected rats, although no such lesion was observed in SCID mice models. Majority of investigations using rodent-nematode model strongly suggested that loss of worm burden from the host could be partly achieved by an increase in mast and goblet cells[35]. Goblet cell secretes mucus considered to serve as a protective function by excluding or trapping worms in immune animals or by hindering intimate contact with the mucosa, thus preventing their establishment. Goblet cell hyperplasia and alteration of the terminal sugars of goblet cell mucins were observed in the expulsion of *Nippostrongylus brasiliensis* from host rats[22]. Mast cells on the other hand, were associated with the expulsion of *Stongyloides ratti*[42]. Highly sulfated glycoconjugates derived from mast cells and goblet cells, act as mucosal surface barrier against Strongyloides worms[22].

The reason why this hepatic parasite would induce such lesions in the small intestine and colon is incomprehensible. Although, TtLES contains glycosaminoglycans[16] that might be a type of glycoconjugate most intestinal helminths secreted as adhesion substances. Goblet and mast cell hyperplasia is the host's response against parasite-derived glyconconjugates to avoid attachment[22].

Conclusions

TtLES products have been proved to induce the digestive tract lesions in this unique phenomenon between hepatic larvae and gut mucosa. Development of hyperplasia is dependent on the volume of product partly influenced by the immune status of the host. It is speculated that larvae-derived factors may have similarities with that of gastrointestinal nematodes and their actions revealed identical host responses.

Host response in gastric mucosa is related with responses to gastric nematode infection. Another speculative idea however regards components of TtLES to have EGF or TGF-α like

actions that induce the hyperplatic lesions. Intestinal response showed some comparable lesions with intestinal nematodes such as *N. brasiliense* and others.

Proliferative studies clarified that in gastric mucosa, initiation of hyperproliferation was in the stem cells by direct initiation of TtLES or indirectly through parietal cell ablation. Massive accumulation of precursor cells occurred due to inhibition of differentiation and maturation into parietal and zymogenic cells. Enteric mucosa did not show increase in proliferating cells but delayed cell cycle seemed to cause villi length increase and mucosal cell hyperplasia.

The bulk of information is still insufficient to fully comprehend the mechanism of gastroenteropathy. Until recently, the focus of interest was on the pathophysiological effects of larvae infection on gut mucosa. Based on the above findings it is suggested that direction of researches should lean towards molecular characterisation of TtLES product components and their interactions with host defence mechanisms. That could provide deep insights on host-parasite relationships and may provide hints about immunomodulatory molecules or the role of helminths in carcinogenesis. Both are significant in greater understanding of the prevention and control of related parasitic diseases.

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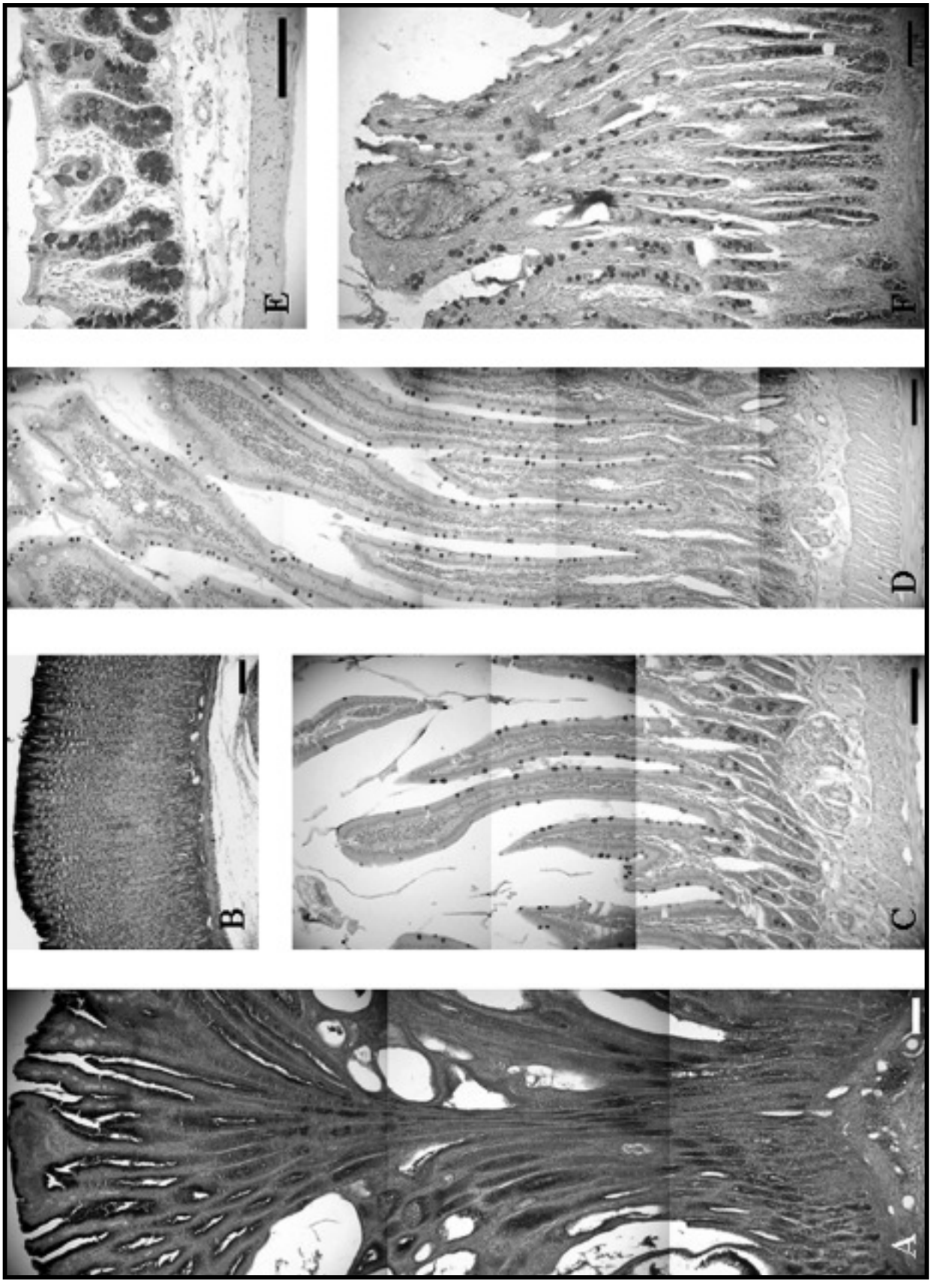

Figure 1 Histological features of the *Taenia taeniaeformis* larvae induced gastroenteropathy stained by alcian blue-periodic acid-Schiff reaction. Hyperplastic mucosa of the gastric gland (A) of an infected rat showing 3 to 4 times thickened when compared to a control gastric mucosa (B). Duodenal epithelia of an uninfected rat (C) is twice shorter compared to the hyperplastic duodenum of an infected rat (D). Colonic mucosa of a control rat (E) is lesser in villi length compared to the colonic mucosa of an infected rat (F). Bars = 100 μm.