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HEMORRHAGIC LESIONS IN STOMACH OF Rhesus Monkey CAUSED BY A PISCINE ASCARIDOID NEMATODE

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ABSTRACT: Within a few hours after being administered to the rhesus monkey (Macaca mulatta), Hysterothylacium type MB larvae penetrated the stomach wall, causing hemorrhage and attracting eosinophils. Inocula of up to 300 larvae, however, did not cause peripheral hypereosinophilia. This species is the first ascaridoid which normally matures in fish that has been shown to penetrate the alimentary tract of a primate. Consequently, human consumption of raw seafood from at least the northern Gulf of Mexico free from infections with Anisakis spp., Phocanema decipiens, or other species that mature in mammals or birds does not necessarily assure freedom from anisakiasis as previously assumed.

Anisakiasis, a term used to include infections by all ascaridoid nematodes having larval stages in aquatic hosts, has become established as a recognizable human disease that causes severe gastrointestinal disorders and even death in some patients (Oshima, 1972; Jackson, 1975; Margolis, 1977; Smith and Wootten, 1978). Nevertheless, Jackson (1975) and others who reviewed the disease did not mention any worms other than larval stages of species in the genera Anisakis, Phocanema, Porrocaecum, and Contracaecum—species whose final hosts are mammals or birds. In contrast, Petter (1969a, b) and Norris and Overstreet (1976) suggested that some species that normally mature exclusively in fishes may infect man. At least one of two species described by Norris and Overstreet (1976), Hysterothylacium type MB (as Thynnascaris type MB, see review of genus by Deardorff and Overstreet, 1981), consistently penetrated the alimentary canal of mice.

Hysterothylacium type MB larvae commonly infect the mesentery and visceral organs of the southern flounder, Paralichthys lethostigma. Infected viscera from recently caught fish were placed in a conical screen fitted into a stemmed, conical glass receptacle filled with 0.80-0.85% sodium chloride. Larvae spontaneously emerged from the viscera, thereby allowing their collection from the bottom of the glass receptacle. Because more than one species of ascaridoid infected the flounder, type MB larvae were selected individually on the basis of their characteristic, blunt, spineless tail bent dorsad and their caecal to ventricular appendage length ratio of 1:14-68. Dissecting and compound microscopes were necessary to confirm the identity of these 1-3-mm-long worms. Within 13 hours after capture of the fish, viable worms were introduced with distilled water into the stomachs of monkeys; the worms were injected through a pediatric feeding tube placed transnasally. Except for the last two monkeys, we did not tranquilize the animals before administering the worms.

MATERIALS AND METHODS

All larval specimens of Hysterothylacium type MB for this study came from the southern flounder, Paralichthys lethostigma. Infected viscera from recently caught fish were placed in a conical screen fitted into a stemmed, conical glass receptacle filled with 0.80-0.85% sodium chloride. Larvae spontaneously emerged from the viscera, thereby allowing their collection from the bottom of the glass receptacle. Because more than one species of ascaridoid infected the flounder, type MB larvae were selected individually on the basis of their characteristic, blunt, spineless tail bent dorsal and their caecal to ventricular appendage length ratio of 1:14-68. Dissecting and compound microscopes were necessary to confirm the identity of these 1-3-mm-long worms. Within 13 hours after capture of the fish, viable worms were introduced with distilled water into the stomachs of monkeys; the worms were injected through a pediatric feeding tube placed transnasally. Except for the last two monkeys, we did not tranquilize the animals before administering the worms.

We used five monkeys (rhesus monkey, Macaca mulatta) in this study: 1 = (98Z), 5½ yr, 5.1 kg, male, colony born (CB); 2 = (OK9), 13 mo, 2.2 kg, female, CB; 3 = (94Z), 6 yr, 4.7 kg, male, CB; 4 = (584C), estimated 5 to 6 yr, 7.6 kg, native born (NB); 5 = (682B) estimated 5 to 6 yr, 6.0 kg, castrated male, NB. Monkey 2 was infected prior to monkey 1. They were all procured, maintained, and used in accordance with the "Guide for the Care and Use of Laboratory Animals" (Institute of Laboratory Animal Resources, National Academy of Sciences—National Research Council) and the Laboratory Animal Welfare Act of 1966, as emended. They exhib-
FIGURES 1–6. Monkey stomach infected with *Hysterothylacium* type MB larvae. 1. Gross hemorrhaging in monkey 2 at 5 hr PI. 2. Larva penetrating toward muscularis mucosae with eosinophils near its anterior and within excavation of monkey 1 at 1½ hr PI. 3. Cross section of larva in gastric mucosa showing eosinophilic inflammatory reaction of monkey 1 at 1½ hr PI. 4. Typical mucosal hemorrhage (arrow) with no blood in adjacent intestinal lumen and no worms evident in section or numerous sections several millimeters adjacent. Section is from monkey 1 at 1½ hr, but represents condition observed at later periods PI. 5. Hemorrhagic mucosa of monkey 1 at 1½ hr PI with cross-sectioned larva. 6. Ulcerated mucosa with inflammation and hemorrhage in monkey 3 at 4 days PI. Note vessel with mostly eosinophils within lumen.
ited good health, no sign of parasites or their eggs, and a negative tuberculin reaction at the time of experimentation. Native-born animals had been maintained for several years under laboratory conditions, and all had been used previously for a variety of other experiments, none involving parasites. During the study, the monkeys were housed indoors and maintained individually in suspended, stainless steel cages. Animals received 9 hr of light daily in an ambient temperature maintained between 18 and 20 C. There were 12 to 15 changes of nonrecirculated air supplied per hour. A commercial diet (Monkey Chow 5038, Ralston Purina Company) was provided twice daily along with unlimited water from automatic waterers.

Animals were sacrificed with pentobarbital sodium solution administered intravenously. Peripheral blood came from saphenous or femoral veins, typically at 0800 hr.

Tissues were fixed in either 10%, phosphate-buffered formalin or Bouin's solution and then processed and stained using standard procedures (Luna, 1968). In addition to examining fresh and sectioned tissue for pathological alterations and worms, we irrigated the peritoneal and thoracic cavities, candled the intestines, decanted the gut contents, and placed the intestine and occasionally other tissues in the cone device described for extracting worms from fish. In one case, we exsanguinated a monkey and filtered the blood for worms.

RESULTS

At necropsy, the stomachs of all the animals but one revealed gross hemorrhage and gastritis. Only monkey 5, which had not received larvae for the preceding 4 wk, had a grossly normal appearing stomach.

Monkey 1 was exsanguinated 1½ hr after receiving about 350 larvae. Gross hemorrhage was evident only in the mucosa of the stomach. Three distinct lesions, approximately 5 x 3 mm, were present along the incisura angularis, whereas smaller ones and diffuse gastritis (mucosal hemorrhaging) occupied most of the body of the stomach.

Monkey 2, given about 200 larvae and examined 5 hr later, had a single, 1 x 2-cm hemorrhagic lesion present in the mucosa of the body of the stomach with four smaller hemorrhagic lesions and diffuse mucosal hemorrhaging in the pyloric region (Fig. 1). A hemorrhagic focus about 1 cm in diameter also was identified in the serosa adjacent to the largest mucosal lesion. In the duodenum, six small, distinct lesions encircled the region near the pylorus.

As seen originally in the syringe, the 400 worms administered to monkey 3 were in two large clumps of about 75 worms each, with the remainder evenly distributed in the water suspension. At necropsy on the fourth day PI, the monkey had seven approximately 1-mm-long, orange-colored, healing ulcers with mucosal hemorrhaging in the body of the stomach. There was no evidence of similar lesions in the duodenum.

Monkeys 4 and 5 were used to investigate the effect of multiple inocula of worms; they showed a marked contrast on gross inspection. Because monkey 4 had vomited many of the initially inoculated worms within 5 min after administration, both monkeys 4 and 5 were tranquilized the following day and presented with enough additional worms so that each had retained a total of about 300 worms. On days 17 and 31, monkey 4 received about 325 and 75 worms, respectively; monkey 5 received distilled water by nasal gastric tube on those days. When necropsied 5 hr following the nasally administered water on day 31, monkey 5, the control, showed no evidence of lesions or mucosal hemorrhage. Monkey 4, given worms, exhibited hemorrhage and gastritis in the body of the stomach at 5 hr, but the lesions were not as extensive as in monkey 1 after the same period of time.

Histologically, the sections exhibited evidence of considerable hemorrhage, with an inflammatory infiltrate consisting of numerous plasma cells, macrophages, and lymphocytes seen mostly in the lamina propria of most sections. Eosinophils occurred conspicuously, but did not constitute a predominant inflammatory cell. However, some blood vessels carried an abundance of eosinophils, with many showing evidence of having undergone degranulation. Sections from the stomach of monkey 1 demonstrated nonsuppurative ulcers. In this monkey, several sections of mucosa revealed nematodes that, at the time of fixation, were alive and heading both toward the muscularis mucosa (Fig. 2) and toward the epithelium. Eosinophils coated most of these worms (Figs. 2, 3) and their excavations, with assumed products of degranulation often surrounding the tunnels left by the worms. Figure 4 (a section of this monkey's stomach) reveals hemorrhage into the mucosa; Figure 5 is similar, but a worm is present. Eosinophils constituted the predominant inflammatory
cell near the anterior of the penetrating worms (Fig. 2) with some neutrophils also present. The histology of the sections of stomach in monkey 2 was similar to that seen in monkey 1; however, no worms could be identified. Most circular excavations, presumably made by the worms, were filled with a fluid or inflammatory exudate. In monkey 3, hemorrhage was still apparent histologically. Numerous fibroblasts and other signs of rapid regeneration were obvious, even though some areas exhibited ulceration (Fig. 6). The muscularis mucosa usually had more eosinophils than did the lamina propria, and there were a few multinuclear giant cells also seen in or adjacent to the muscularis mucosa.

The stomach of monkey 4 had a more extensive inflammatory reaction in the mucosa (Figs. 7, 8) than did that of monkey 5 and was the only one of the pair to demonstrate mucosal hemorrhage. An abundance of histiocytes containing multiple inclusions was present. There were several, presumed worm excavations identified in the mucosa, but no worms were seen in any of the numerous samples examined.

To enable a comparison between Hysterothylocalicum type MB in the monkey and Anisakiasis.
TABLE I. Components of blood in relation to oral inoculation of larval *Hysterothylacium* type MB. Italicized figures (*) are those obtained 6 hr postinoculation (PI) except for those with an asterisk (*), which are 3 hr PI.

<table>
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<tr>
<th>Day</th>
<th>Time</th>
<th>Monkey</th>
<th>RBC × 10⁶</th>
<th>WBC</th>
<th>Neutrophils</th>
<th>Lymphocytes</th>
<th>Monocytes</th>
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<td>8,830*</td>
<td>9,450*</td>
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<td>1,776</td>
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*Hysterothylacium* sp. in the stomach of the miniature pig, J. W. Bier provided us sectioned material of the latter at 4 and 7 days PI. The large *Anisakis* sp. did not penetrate through the stomach wall, but attached, became surrounded by a distinctive band of eosinophils (Fig. 9), and soon died and became consumed within an eosinophilic granuloma (Fig. 10).

No worms could be filtered from the blood of monkey 1, nor were any recovered from any of the monkeys by washing the thoracic and peritoneal cavities with saline. From intestinal contents of monkeys 1-4, a single active worm was recovered from the gut contents in the proximal intestine of monkey 1, and, after 20 hr, we removed four dead and two live worms from intestinal contents of monkey 2. Other than those and the larvae in stomach tissue of monkey 1, we were unable to find any worms. We examined stomach, intestine, liver, lungs, and diaphragm with transmitted light. Also, no worms escaped when these organs were placed in the cone with saline overnight.

Complete blood counts always changed following administration of larvae, as illustrated by monkey 4. The counts for monkey 4 and those for monkey 5 are compared in Table I. There was little variation in the red blood cell (RBC) count in spite of hematocrit levels, which appeared to drop about 2 to 5 percentage points within 2 or 3 days PI; values ranged between 39 and 46%. There was a conspicuous increase in the white blood cell (WBC) count immediately following each inoculation of worms. Figure 11 illustrates the percentage rise of peripheral neutrophils and drop in concurrent lymphocytes following the inoculation. Total counts of each WBC type per cubic centimeter tabulated in Table I also suggest an apparent increase in the peripheral monocyte count and an apparent decrease in peripheral eosinophils. These and other patterns in blood counts for the first three monkeys given a single inoculum were all similar to those noted above.

**DISCUSSION**

We have demonstrated clearly that *Hysterothylacium* type MB larvae are capable of penetrating the upper gastrointestinal tract of primates. Grossly, hemorrhaging was obvious in the stomach and proximal duodenum of monkeys administered worms at least 1½ hr to 4 days previous to examination. Extensive lesions probably correspond to the sites where numerous worms invaded; *Hysterothylacium* type MB typically clump together in saline when not encysted. When we dispersed clumps prior to administration, gastritis appeared more widespread.
fed each of six Taiwan monkeys 100 Anisakis sp. larvae and obtained similar results. Only at 6 hr and 2 days were worms found in the lumen or wall of the stomach. When he examined monkeys from 4 to 8 days PI, he recovered larvae primarily from the greater omentum. Hsieh and Chen (1970) noted that when 200 specimens of Anisakis sp. were fed to the Taiwan monkey, they penetrated the stomach wall and esophagus by 6 hr.

Penetration sites vary according to species of both host and parasite. According to a review of "codworm" (Phocanema decipiens) infections in humans (Margolis, 1977), almost all of the 46 confirmed or presumed cases were confined to the stomach, whereas intestinal invasion, unknown for P. decipiens in man, commonly occurred in the more than 1,200 known human cases caused by Anisakis spp. Whereas codworms typically partially penetrate the stomach of the miniature pig (Jackson et al., 1976) and other animals, Anisakis sp. causes a more severe and persistent host reaction and completely embeds in the gastric wall (Bier et al., 1976).

Histologically, we noted an abundance of inflammatory cells consisting primarily of eosinophils surrounding worms at 1½ hr PI, hemorrhage and some edema in mucosal tissue from 1½ hr to 4 days, and infiltration of inflammatory cells in some regions for at least 5 days. Some observations may not reflect responses to the worm. Lymphatic nodules occurred abundantly in all stomachs, often extending into the submucosa. On the other hand, according to Oishi et al. (1974), the codworm had a more potent pathogenic capacity than Anisakis sp. in rabbit stomach.

Histologically, we noted an abundance of inflammatory cells consisting primarily of eosinophils surrounding worms at 1½ hr PI, hemorrhage and some edema in mucosal tissue from 1½ hr to 4 days, and infiltration of inflammatory cells in some regions for at least 5 days. Some observations may not reflect responses to the worm. Lymphatic nodules occurred abundantly in all stomachs, often extending into the submucosa. These are considered normal. Ulceration and erosion of the mucosa and abundance of inflammatory cells in the lamina propria, epithelium, and muscularis mucosae probably in some, but not all, instances reflect ascaridoid infections, especially when blood vessels adjacent to the lesion or focus contained many inflammatory cells. In many cases, however, those features probably resulted from previous experimentation, confinement, or other factors.

Infections with Hysterothylacium type MB in the rhesus monkey differ from those with the relatively large larval P. decipiens and
Anisakis spp. in man, pigs, and other mammals, primarily because the worm is smaller and passage through host tissue was rapid. Larvae move slowly enough to allow eosinophils to accumulate about them, but fast enough to be absent from abundant samples of tissues examined from stomach and duodenum by 5 hr PI. We saw no amorphous eosinophilic "hyaline caps"; such material occasionally occurs about the head of penetrating larval ascaridoids and singly in granulation tissue in both natural and experimental hosts (e.g., Liu and Edward, 1971; McClelland, 1980). In mice, Hysterothylacium type MB occurred at all levels of the stomach wall by 4 hr PI, and by 8 hr most had died in the submucosa (Ebert and Norris, in prep.). Where the worms go in the monkey and how long they live there were not determined, but at 5 hr PI none could be recovered from stomach tissue, intestinal tissue, filtered blood, or a saline wash of the body cavities. Few occurred in intestinal contents. By that time an inflammatory exudate had filled the worms' excavations. Thus, the condition contrasts with that produced by Anisakis spp. and P. decipiens where the appearance of signs is delayed.

Accumulation of eosinophils about the penetrating larvae at 1½ hr, although unusual for most foreign bodies in tissues, has a precedent with related worms. Tanaka and Torisu (1978) injected the soluble extract of larvae of Anisakis sp. into normal guinea pigs and observed eosinophils that accumulated at the site of injection. With the concentration used, they noted that accumulation started at 1 hr and peaked at 8 hr PI. Anisakis sp. in the stomach of a miniature pig had a defined accumulation of inflammatory cells including many eosinophils surrounding it and only slight eosinophilic infiltration in tissue immediately adjacent at day 4 (Fig. 9), which in another case at day 7 was intense in and adjacent to a dead specimen (Fig. 10). Eosinophilic granulomas have been diagnostic for human cases of anisakiasis since that disease has been recognized (e.g., Van Thiel et al., 1960; Van Thiel, 1962; Asami et al., 1965). Moreover, perhaps the pig provides a more humanlike model than some or all monkeys. In the Taiwan monkey, Anisakis sp. penetrated through the stomach within 4 days, not producing extensive granulomas (Wu, 1970). After that period, Wu noted fibrotic granulation tissue about larvae in the viscera, but eosinophils were never abundant.

Anisakids can stimulate vomiting. As an example, Nagano (1974) noted that humans, often in severe epigastric pain, vomited worms. When Margolis and Beverley-Burton (1977) administered 15 or 30 larval A. simplex to mink in a bolus, most mink within an hour started to shiver, vomit, and defecate until the larvae were expelled. In contrast, when they injected mink with sodium pentobarbital, some of the lots of 5 or 15 worms administered in gelatin capsules would penetrate. In one instance only did any of our monkeys, monkey 4, vomit, and we sedated him the following day so as to insure introduction of additional worms.

All the larval ascaridoids discussed above have mechanisms for invading tissues. When an infected host is eaten, the worm excysts and has the ability to invade and infect a variety of predatory fishes and crustaceans without maturing in them (e.g., Smith, 1974). Adult members of Hysterothylacium spp. are not known to penetrate their piscine definitive hosts; however, several related species of Goezia and Icheringascaris inquies do (Dear-dorff and Overstreet, 1980).

Larvae of most species of Hysterothylacium probably do not invade mammals as does type MB. Type MA did not invade mice (Norris and Overstreet, 1976) and neither did a third species of Hysterothylacium (Norris, Overstreet, and Deardorff, unpubl. data). Larvae identified as T. aduncum from Sardina pilchardus caught off France have been implicated in human disease (Petter, 1969a, b), but such larvae from these and other hosts did not invade a variety of experimental mammalian hosts (Tolgay, 1965; Vermiel et al., 1975). On the other hand, a larva identified as Contracaecum sp. 2 from a stomach lesion in a stray dog from Japan had an intestinal cecum shorter than its ventricular appendage (Kita-yama et al., 1967), suggesting that it may be a species of Hysterothylacium as opposed to Contracaecum sensu lato. Ko (1976) observed that larval specimens of Echinoccephalus sinensis, a gnathostome nematode that matures in the eagle ray, collected from August to October, invaded and caused lesions in monkeys
and cats, whereas specimens collected during other months did not penetrate those hosts. A similar acclimation phenomenon may also exist for some *Hysterothylacium* spp.

Temperature could affect (but probably did not) the virulence of *Hysterothylacium* type MB. The inflammatory response at 5 hr PI in monkey 4 on 22 November 1978 was not as intense as in monkey 2 on 12 May 1978 even though monkey 4 had been challenged with worms twice. The first infection, however, involved about 200 worms compared to 75 larvae in the latter, suggesting that number of worms has more influence than a hypersensitivity reaction, if one exists.

The response of blood cells to the challenge generally was as expected for an inflammatory response. Segmented neutrophils increased, whereas lymphocytes decreased in the circulating blood apparently because they were invading the lesions. Even though numbers were relatively low, counts of peripheral monocytes tended to increase and those of eosinophils tended to decrease following all inoculations. The slight variations for most counts from the normal following sham inoculations in monkey 5 may be explained by the time of day during which blood was sampled (Table I).

For a parasitic worm, especially one that produces substances attracting eosinophils, we expected a higher, prolonged level of peripheral eosinophilia. Even the relatively high level in monkey 5 (up to 20%) was normal for that individual. In contrast, hyper eosinophilia reaching a peak at 2 to 3 wk PI characterized macaque monkeys experimentally infected with larvae of the ascaridoid *Toxocara canis* (e.g., Tomimura et al., 1976). The number of larvae of *T. canis* administered totaled many thousand, and the resulting eosinophilia was correlated at least partially with the number. Natural human accumulation of such massive doses of *Hysterothylacium* larvae is highly unlikely, especially when compared with that of *T. canis*. Most larval *T. canis* in the rhesus monkey, and presumably man, infect the liver and live there for at least 7 years (Beaver, 1962). We did not find *Hysterothylacium* type MB in squash preparations of liver or from material placed in cones. On the other hand, possibly they invaded the liver or elsewhere and died quickly, thereby not eliciting a peripheral eosinophilia. Most die quickly within mice. Consequently, if *Hysterothylacium* type MB larvae react similarly in man and monkey or even penetrate man at a slower rate, the primary danger in moderate infections, except in individuals especially hypersensitive to such infections, lies in misidentification and treatment of the disease. Eosinophilic gastroenteritis is typically thought of as a specific disease (Leinbach and Rubin, 1970) and not related to parasitic infections. Perhaps ascaridoids or their products are responsible in some cases, and perhaps the use of *Hysterothylacium* type MB or another ascaridoid can aid in better understanding the role of the eosinophil. With that knowledge, as suggested by Johnstone and Morson (1978), the precise nature of eosinophilic gastroenteritis and other diseases might be more easily determined.

**ACKNOWLEDGMENTS**

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**LITERATURE CITED**


