

PATHOLOGY AND PATHOGENESIS OF HUMAN GNATHOSTOMIASIS

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In human gnathostomiasis, the migratory subcutaneous swelling or edema is regarded as the characteristic clinical sign even though visceral involvement is also noted in many reported cases. The causative nematode, *Gnathostoma spinigerum*, with its life-cycle, has been thoroughly studied by several authors but the anatomic pathology produced by the worm in the subcutaneous tissue and the visceral organs has been inadequately worked out. Recently, two cases of human gnathostomiasis came under our observation so that we wish to present our pathological observation and a discussion on the pathogenesis together with the review of the literature on this subject.

Reviewing of the literature revealed that in many cases, as reported by several authors, the mixture of subcutaneous and visceral involvements was present. The subcutaneous swelling or edema usually subsided without residual noticeable lesion, however, residual hard nodules were noted in a few cases. These subcutaneous lesions were so infrequently resected and histologically examined that detailed morphologic descriptions were lacking. In a very brief manner Daengsvang⁽⁵⁾ described both subcutaneous swelling and visceral lesions to show areas of degeneration and necrosis together with heavy infiltration by a great number of eosinophilic and neutrophilic polymorphonuclear

leukocytes associated with "hemorrhagic exudate" and mononuclear cells at some places. And, he stated further that the tissue which was continuously affected by the worm usually showed fibrous formation with much cellular infiltration. Prommas and Daengsvang⁽⁸⁾ reported the microscopic observation of a residual hard subcutaneous nodule to show tunnel-like spaces containing necrotic tissue surrounded by tissue extensively infiltrated by eosinophils, mononuclear cells, some fibrin and occasional red blood cells. Bovornkitti and Thandhanand⁽²⁾ reported the pathology of the residual skin nodule in another case clinically diagnosed as gnathostomiasis to show a chronic granuloma infiltrated with eosinophils and a few giant cells. There were no worms noted in both instances. In another similar case, Kangsdal and Bovornkitti⁽⁷⁾ reported a residual skin nodule as suggestive of a "parasitic cyst". Visceral involvement particularly of the brain and spinal cord, the worm produced marked hemorrhagic phenomenon as reported by Chitanondh and Rosen⁽³⁾ and Punyagupta, et al.⁽⁹⁾ Microscopically, they noted hemorrhages, and necrotic tracks associated with marked generalized vascular congestion with perivascular infiltration of lymphocytes, plasma cells and eosinophils. There were no "eosinophilic granulomas" nor "abscesses" seen in

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these cases. Daengsvang⁽⁵⁾ reported the gross lesion of the omentum in his four abdominal-typed patients as a smooth hard and more or less rounded tumor but no detailed microscopic observation was given. Recently, Punyagypta, et al.⁽⁹⁾ reported clinical manifestation of a group of patients believed to be caused by third stage larva migrating through the intestines and liver.

Case Reports

Our two cases are as the following :-

Case 1. A 33 year-old, married, female Thai teacher started to have a small amount of melena one month prior to her admission. Four days later she had an intense abdominal pain followed by the passage of a large amount of melena and she fainted. A blood transfusion was given by a physician and she recovered. Then, a palpable mass in her right iliac

fossa was found, and operation was advised. On admission to the hospital no other physical abnormalities other than the abdominal mass were noted. The routine laboratory examinations were normal. No past history of migratory swelling was recorded. At operation, a protruding sessile submucosal mass was noted in the cecum together with enlarged mesenteric lymph nodes. A right half colectomy was performed.

The gross examination of the specimen showed a bulging, intramural, ill-defined, firm nodule, approximately 6.0 cm. in greatest, diameter, in the cecum (Figure 1). The elevated intra-luminal surface was covered by an intact but hemorrhagic cecal mucosa. The nodule was made up of gray tissue with a small hemorrhagic area. The lesion involved all layers of the wall and the serosa was markedly thickened with adherent omental tissue. The ileo-colic lymph nodes measured up to 3.0 cm. in greatest, diameter.

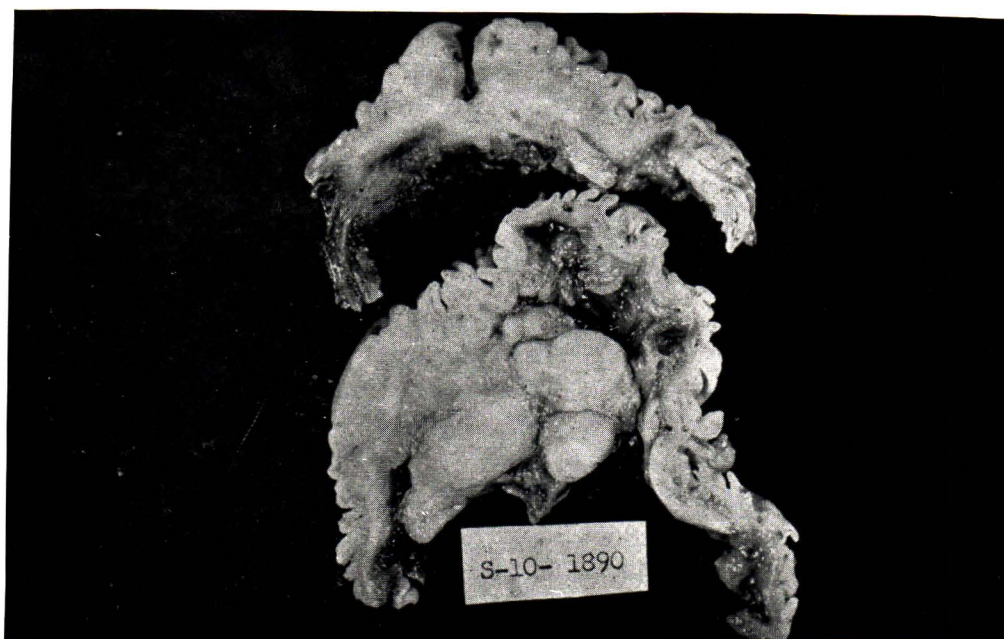


Figure 1. Cecum showing intramural nodular mass and enlarged regional lymph nodes.

Microscopic examination of the lesion revealed cross sections of an embedded worm having spiny cuticles located in the cecal submucosal layer. (Figure 2). The worm was partially encased by finely granular acidophilic material surrounded by a very heavy infiltrate of eosinophils with very few plasma cells. Localized hemorrhage and fibrin were noted at one area closed to the worm. In association with the cellular infiltration surrounding the worm, endothelial cell proliferation with newly formed capillaries were present. In other parts, the lesion was composed of proliferating or hyalinized fibrous connective tissue with numerous capillaries and blood vessels diffusely infiltrated by eosinophils, lymphocytes, plasma cells and occasional histiocytes (Figure 3). The arteries showed frequently onion-like perivascular fibrosis. Groups of pigment-laden macrophage were scattered throughout as well as follicles of lymphoid cells. Another striking feature was the presence of track-like granulomatous reaction. The central space of some tracks was made up of collections of degenerating and necrotic eosinophilic leukocytes and few neutrophils in some places at their rims. There were depositions of intensely acidophilic granular and fibrillary materials. These were surrounded by epithelioid cells with occasional multinucleated giant cells of foreign body or Langhan's type (Figure 4). Charcot-Leyden crystals were infrequently seen in the epithelioid layer as well as fibrinoid-like change. The epithelioid cells were in turn surrounded by fibrous tissue layer. In some tracks,

the central necrotic tissue was less conspicuous but the fibrous layer became prominent and was collagenized or hyalinized. The serosa of the cecum was markedly thickened by hyalinized connective tissue with a large number of congested blood vessels. The mesenteric lymph nodes showed follicular hyperplasia associated with marked eosinophilic infiltration within medullary cords and the sinusoids.

A post-operative skin test for *Gnathostoma spinigerum* was positive.

Case 2. A 63 year-old, married male, Thai farmer developed a gradually growing mass in his right testis about one month prior to his hospital admission. No past history of migratory swelling was recorded. On admission, physical examination disclosed an abnormality in his right scrotal sac only. An oval tender mass, 8 × 5 × 5 cm. was palpated but the normal testicular outline could not be determined. Inguinal lymph nodes were considered to be enlarged bilaterally. The hemoglobin was 8 gm% and white blood cell count 10,000/cu. mm. with 70% neutrophils, 4% eosinophils, 25% lymphocytes and 1% monocytes. A right orchidectomy was performed.

The gross examination of the specimen revealed the testis to be moderately enlarged by the presence of an ill-defined, irregularly shaped nodular mass 2.0 cm. in greatest dimension involving the head of the epididymis and the testicular proper. The cut surface of the mass was light gray with a central hemorrhagic area (Figure 5). An embedded worm was noted under a dissecting microscope in the vicinity of the hemorrhagic area. The testis also exhibited multiple abscess-like foci.

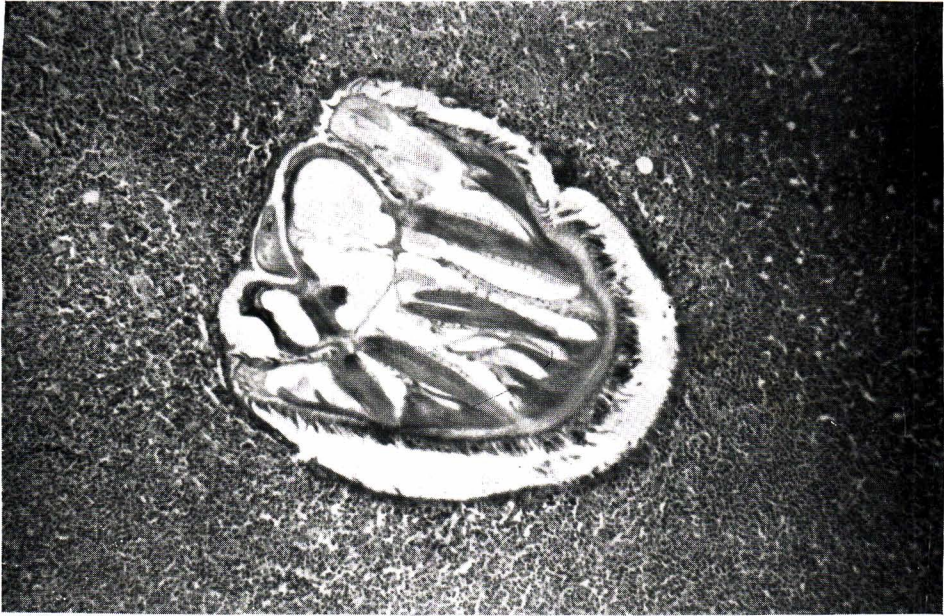


Figure 2. Photomicrograph showing cross section of a worm having spiny cuticles in the cecal submucosal layer.

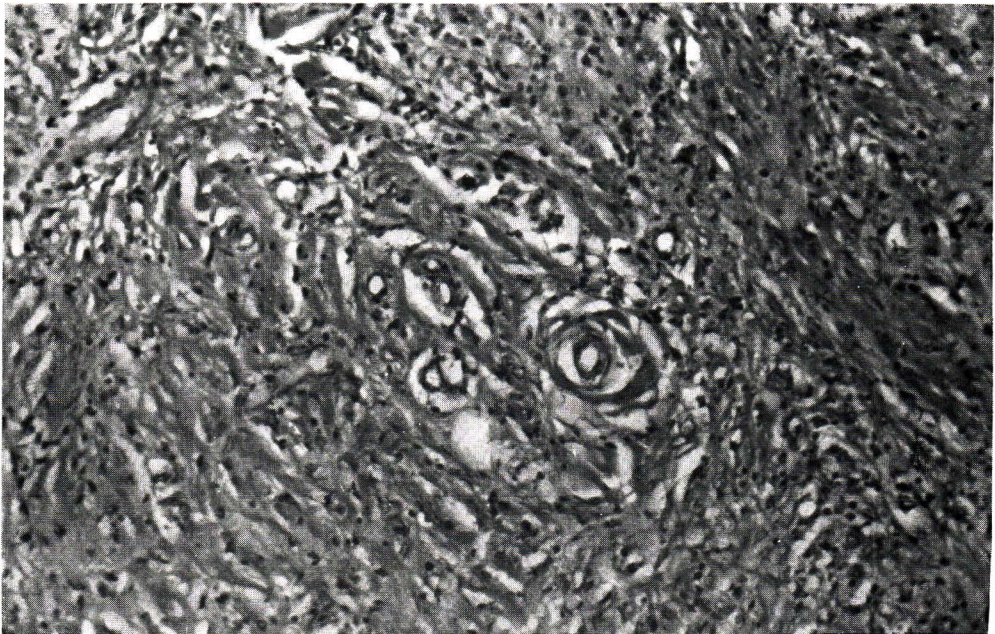


Figure 3. Photomicrograph showing proliferating and hyalinized fibrous connective tissue with numerous capillaries and blood vessels infiltrated by eosinophils, lymphocytes, plasma cells and occasional histiocytes.

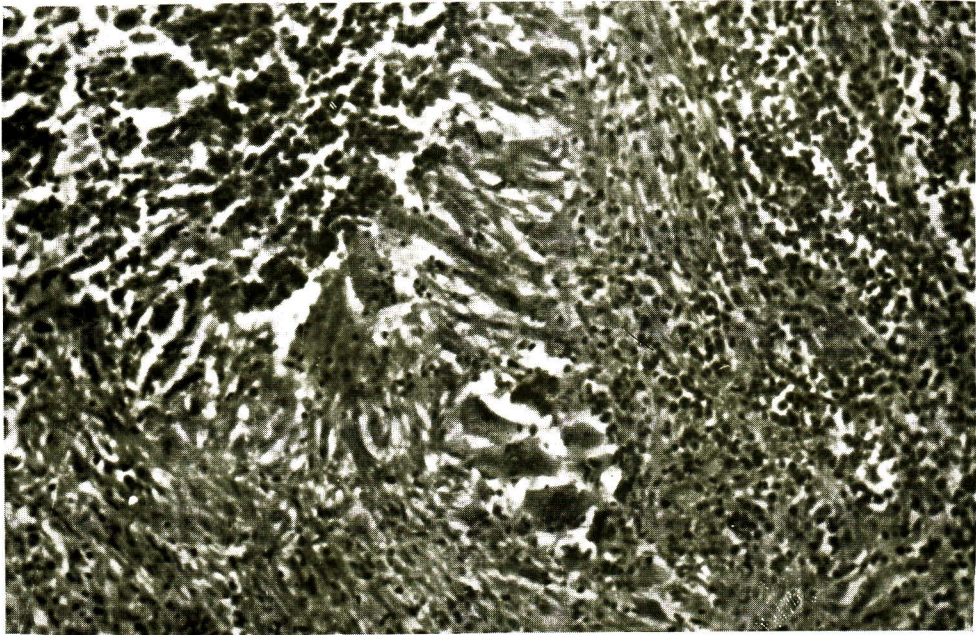


Figure 4. Photomicrograph showing acidophilic granular and fibrillary materials surrounded by epithelioid cells with multicucleated giant cells.



Figure 5. Testicle showing an ill - defined irregularly shaped mass with central hemorrhage.

Microscopic examination of the lesion disclosed tangential sections of a spiny-cuticled worm (Figure 6) partially encased by a thin layer of degenerated and necrotic neutrophilic and eosinophilic leukocytes with fibrinous masses. Fresh hemorrhage was noted at one area closed to the worm. Around the worm and necrotic tissue, the tissue was heavily infiltrated by eosinophilic leukocytes together with a smaller number of plasma cells and lymphocytes. Endothelial cell proliferation with newly formed capillaries and young fibrocytic cell proliferation were conspicuously noted at the periphery of the cellular infiltrated areas. In most part, the lesion was made up of collagenized and hyalinized fibrous connective tissue diffusely infiltrated by eosinophils, plasma cells, lymphocytes and occasional histiocytic cells. Scattered follicles of lymphoid cells were present. Blood vessels were numerous and congested. Some small arteries showed onion-like perivascular fibrous thickening.

A few larger arteries exhibited eosinophilic endarteritis, thrombosis with organization and recanalization (Figure 7). Against this background, there were several track-like abscesses in which no worm was seen. The track wall showed organization and some tracks revealed granulomatous reaction. The central space of these contained intense acidophilic granular material surrounded by epithelioid cells and occasional multinucleated giant cells of foreign body or Langhan's type. Fibrous connective tissue layers around these tracks were often infiltrated by a large number of eosinophilic cells many of which were degenerated with loss of cell membrane. Charcot-Leyden crystals, many being inside phagocytic cells in the fibrous layer were noted as well as fibrinoid-like change. An eosinophilic abscess was noted in the lesion. Multiple abscesses were seen among

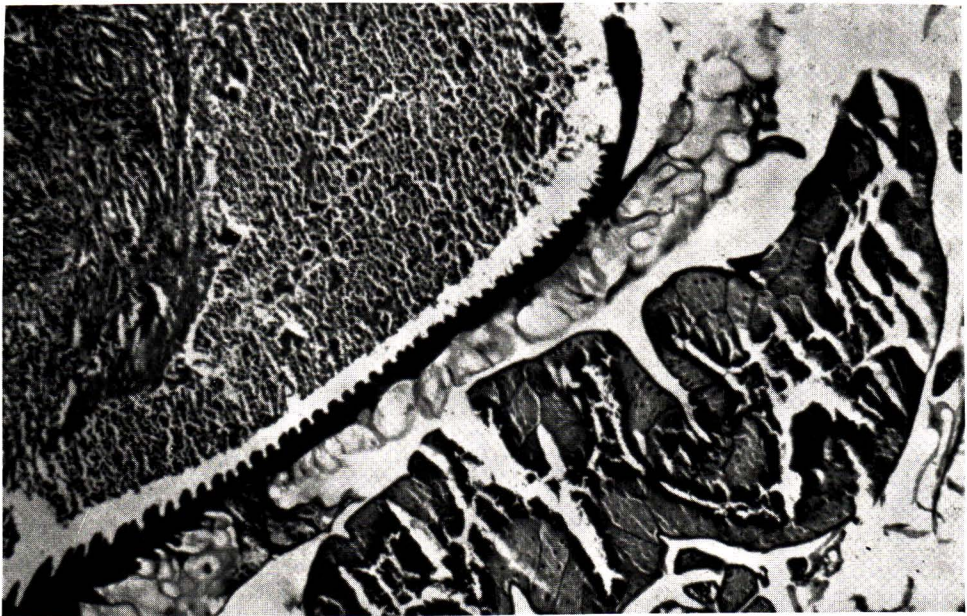


Figure 6. Photomicrograph showing tangential section of a spiny cuticled worm.



Figure 7. Photomicrograph showing endarteritis, thrombosis with organization and recanalization.

seminiferous tubules. The intertubular tissue exhibited marked cellular infiltration chiefly of eosinophilic leukocytes.

Discussion

Clinico-pathological Manifestation :
It can be postulated from the review of reported cases that there are three different types of cases as follows :-

Type I. This consists of cases showing migratory subcutaneous swellings which subsided spontaneously leaving no residual lesions or residual hard skin nodules. The fate of the parasite in these cases, if spontaneous or surgical expulsion did not occur, is not precisely known.

Type II. In this group are cases which at first exhibited migratory subcutaneous swellings which subside and then followed by one or more visceral

organs involvement. The parasites usually become more or less stationary in the organ affected. There may or may not be nodular masses detected depending on the nature of the organs involved.

Type III. These are cases in which there are no history of migratory subcutaneous swelling but present from the beginning as a visceral nodular mass as illustrated by the two cases reported above.

Of all types, the worm probably migrates from the stomach and through the liver to the affected sites as suggested by Sagara,⁽¹⁰⁾ and Hirakawa.⁽⁶⁾ And, this brings to the possibility of another clinical syndrome designated recently by Pungyaku, et al.⁽⁹⁾ as "larval gnathostomiasis"

In our case 1, where the lesion was located in the wall of the cecum, the histopathological study suggested the pathway of parasitic migration from the serosal layer toward the cecal mucosa because the older granulomatous reaction

with marked fibrosis were observed in the serosa and muscular layer. Diagrammatic presentation of our concept of clinicopathological types is shown in figure 8.

Anatomic Pathology: The histopathological change in the lesion of migratory subcutaneous swelling was supposedly characterized by track-like tissue necrosis with hemorrhage and a heavy infiltrate chiefly of eosinophilic leukocytes as reported by Prommas and Daengsvang.⁽⁸⁾ This could be designated as an acute exudative form and was also encountered in the visceral organs particularly in the brain and spinal cord in patients of Type II as described by Chitanondh and Rosen,⁽³⁾ and Punyagupta, et al.⁽⁹⁾ Healing process of this form was probably by resolution leaving no noticeable residual lesion except in the central nervous system where encephalomalacia might be noted.

The visceral lesion in Type III or Type II and probably the residual skin nodule in Type I was characterized by both acute exudative and chronic sclerosing granulomatous changes sometimes with arteritis, as illustrated by our two case reports. It is obvious that the healing of this mixed form will result in scar tissue formation. How long the parasite can be alive in such a lesion is not known. It is conceivable that the activity of the tissue change will cease after the death of the worm. The draining lymph nodes from all types exhibited certain changes as shown by our case 1.

Pathogenesis: As to the mechanism of tissue reaction in human gnathosto-

miasis, it is apparent that two separated processes are involved as suggested by Punyagupta, et al.⁽⁹⁾ One of these are the direct mechanical injury to the tissue resulting from the migration of a spiny cuticled worm. As the worm migrates, the tissue is damaged and destroyed producing track-like spaces together with hemorrhage and acute fibrinopurulent inflammation. However, associated inflammatory change might be the result of a toxic effect. The other mechanism is probably an immune reaction as manifested by peripheral eosinophilia, diffuse eosinophilic infiltration, eosinophilic abscess, fibrinoid change and granulomatous inflammation together with eosinophilic endarteritis. The non-vascular changes in these cases are quite similar to the allergic granulomatosis as described by Churg and Strauss⁽⁴⁾ and also found in cases of visceral larval migrans and other nematode infestations. It was demonstrated by Ando⁽¹⁾ that the positive skin test reaction clinically employed for the diagnosis of this disease was caused by the protein fraction separated from the extract of larval or adult *G. spinigerum*.

The endarteritis in our cases is quite unique. It is unlike the vascular change associated with bronchial asthma as described by Churg and Strauss.⁽⁴⁾ However, we suspect that immunological reaction has a role in its pathogenesis.

The healing process of nonvascular lesion is by scar tissue formation, so that a hard nodule might be left after the worm was dead or migrated to other sites.

The diagram of the tissue reactions and their pathogenesis is shown in figure 9.

CLINICO-PATHOLOGICAL TYPES OF GNATHOSTOMIASIS

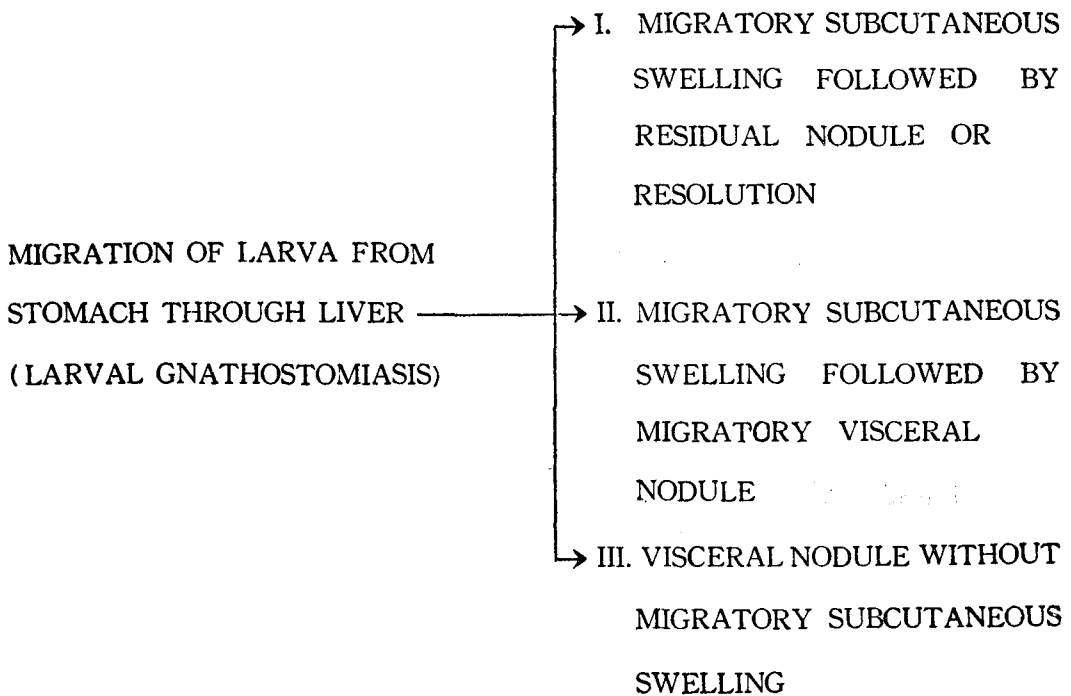


Figure 8. Diagram showing types of clinico-pathological cases of Gnathostomiasis.

PATHOGENESIS AND PATHOLOGY OF SUBCUTANEOUS AND VISCERAL LESIONS IN HUMAN GNATHOSTOMIASIS

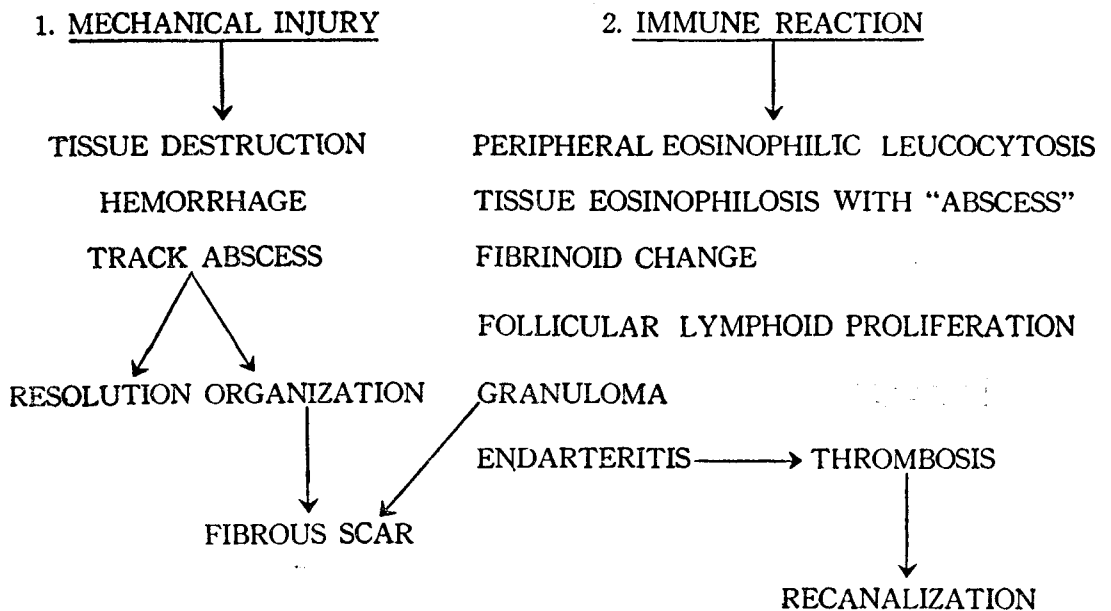


Figure 9. Diagram showing pathogenesis and pathology of Gnathostomiasis.

Summary :

A review of pathological manifestation in cases of human gnathostomiasis was presented with an addition of two new case reports.

It was proposed to classify the clinical cases into three different types depending on clinical and pathological manifestation.

The tissue changes in its acute phase were characterized by granulomatous tracks, eosinophilic infiltration, endarteritis and proliferation of lymphoid tissue.

The pathogenesis of those changes was believed to be the result of mechanical injury from the worm itself and the immune reaction associated with host-parasite interaction.

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