J Korean Med Sci 2002; 17: 686-90
ISSN 1011-8934

The First Human Case of Hepatic Dirofilariasis

Most of human dirofilariasis are pulmonary or subcutaneous infections, but there have been a few reports of human dirofilariasis in unusual sites, such as large vessels, mesentery, peritoneal cavity, and spermatic cord. We present the first case of human hepatic dirofilariasis, which was surgically diagnosed. A 39-yr-old man without any evidence of systemic symptom was found incidentally to have a hepatic nodule during routine physical check-up. The histologic findings of the resected lesion showed a granulomatous lesion with central necrosis containing up to 35 transverse sections of a nematode, ranging 30-80 μm in diameter. Thin (1.5-5 μm) cuticle with transverse striations surrounded polymyarian and muscle bundles occupied a sixth of both sides of outer body cavity. Central portion of the body cavity was occupied with an intestine-like tubular structure and a larger reproductive tube. These microscopic findings were consistent with degenerated *Dirofilaria immitis*. Antibody test by enzyme-linked immunosorbent assay for patient serum reacted positively against adult *D. immitis* antigen.

Key Words : *Dirofilaria immitis; Nematoda; Liver; Human*

Min Kyung Kim, Chul Hwan Kim, Beom Woo Yeom, Seong Hwan Park, Sang Yong Choi*, Jong Sang Choi

Department of Pathology and Department of General Surgery*, Guro Hospital, Korea University College of Medicine, Seoul, Korea

Received : 4 June 2001
Accepted : 8 October 2001

Address for correspondence
Jong Sang Choi, M.D.
Department of Pathology, Korea University College of Medicine, 126-1 Anam-dong 5 ga, Sungbuk-gu, Seoul 136-705, Korea
Tel : +82.2-920-6145, Fax : +82.2-923-1340
E-mail : jongchoi@kumc.or.kr

INTRODUCTION

Dirofilaria immitis and *D. repens* are common nematodes of dogs in many parts of the world, especially in the United States, southern Europe, Australia, and Japan (1). Other mammals, including cat, fox, muskrat, wolf, otter, and sea lion also serve as natural hosts. The coiled adult worms in canine hosts form tangled masses in the right ventricle and pulmonary arteries while microfilariae circulate in the blood (2). In dogs, there are a few reports of hepatic nodule and granulomatous hepatitis caused by dirofilariasis (3, 4).

Most humans dirofilariasis have been found to be caused by infection with immature worms, which are transmitted from infected animals by mosquito bites. Abundance of vector mosquitoes and microfilaraemic dogs are, therefore, the important risk factors of human infections, in which *D. repens* gives rise to subcutaneous nodules and *D. immitis* does to pulmonary nodules (2). By analyzing over 448 cases of human dirofilariasis (1, 5), most of them are pulmonary or subcutaneous infections but there have been a few reports of human dirofilariasis in unusual organs, such as large vessels, mesentery, peritoneal cavity, and spermatic cord (6-9).

We report a case of surgically diagnosed human hepatic dirofilariasis, which is the first human hepatic *D. immitis* infection to our knowledge.

CASE REPORT

Clinical findings

A 39-yr-old man visited Guro Hospital for routine physical check-up and was found to have a hepatic subcapsular hypoechoic nodule (2×1.3 cm) in the right lobe by abdominal ultrasonogram. The patient was healthy without any history of recent illness. He has no history of traveling abroad. The patient had a history of acute hepatitis 15 yr earlier. Abdominal computed tomography (CT) showed a well-demarcated nodule with homogeneous low density on aortoportogram phase (CTAP) (Fig. 1A) and a round nodule with peripheral enhancement on hepatic arterial phase (CTHA) (Fig. 1B). Celiac and superior mesenteric artery angiography showed no remarkable abnormal vascularity (not shown). These radiologic findings suggested nonspecific hepatic nodule in the segment VI. Superselective right hepatic artery and inferior division of celiac angiography showed no tagging on lipiodol infusion. These findings suggested that the nodule be a benign lesion.

Peripheral white blood cell count revealed 7.6×10^9/L with 1.7% of eosinophils, hemoglobin 16.0 g/dL, and hematocrit 45.4%. Platelet count was 159×10^6/L. Liver function tests revealed elevated levels of liver enzymes. AST was 100 IU/L (normal range: 8-33), ALT was 138 IU/L (normal range: 8-

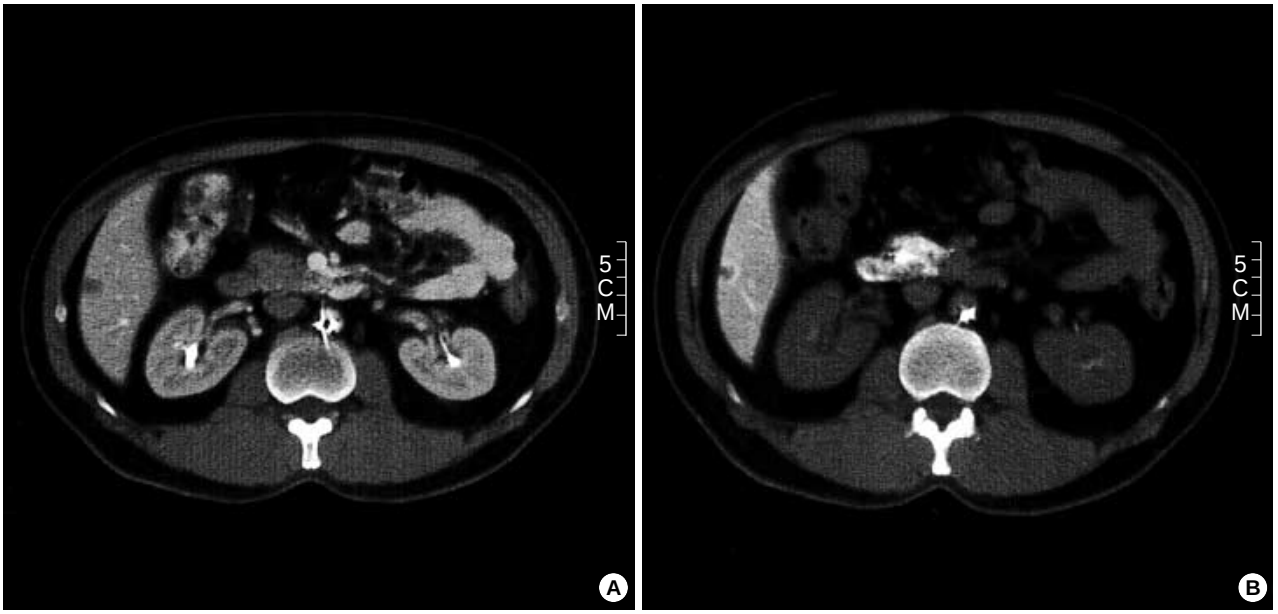

Fig. 1. Abdominal computed tomography. Aortoportogram phase (CTAP) shows a well-demarcated nodule with homogeneous low density (A). Hepatic arterial phase (CTHA) shows round nodule with peripheral enhancement (B).

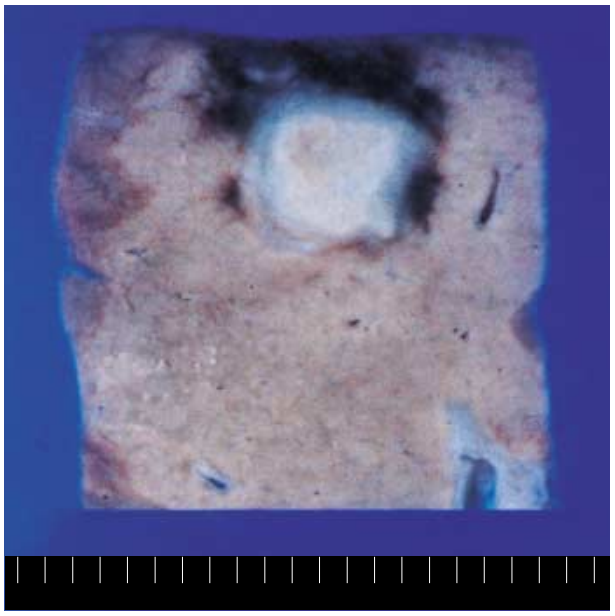

Fig. 2. Cut surface of resected liver. The lesion shows central geographic necrosis surrounded by fibrotic tissues.

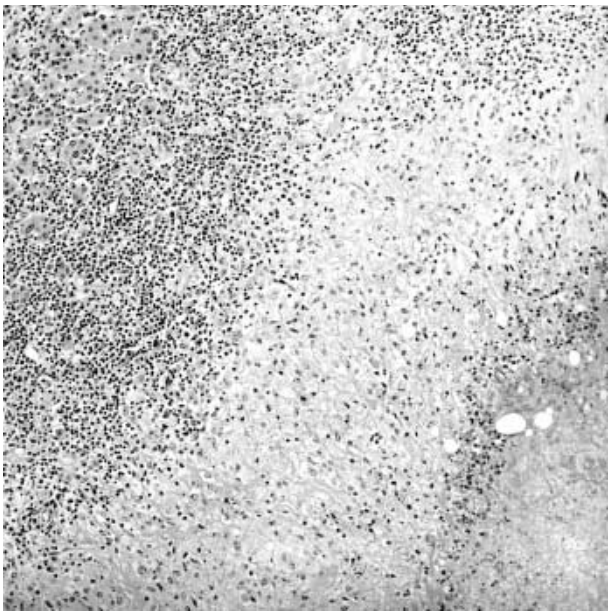

Fig. 3. Coagulative necrosis (in the right lower corner) is rimmed with granulomatous inflammation, in which mixed infiltrates of plasma cells, lymphocytes, and eosinophils are evident (in the left upper corner) (H&E, × 100).

36), and alkaline phosphatase was 86 IU/L (normal range: 25-120). Total bilirubin was 1.19 mg/dL. Radioimmunoassay results for hepatitis virus were positive for anti-HBs antibody and negative for HBs antigen, HBe antigen, anti-HBe antibody, and anti-HCV antibody. Serum α-fetoprotein level was 1.0 ng/mL. The patient volunteered the resection of segment VI to rule out any possibility of malignancy.

Pathologic findings

Cut surface of the resected liver showed a well-demarcated, yellowish lobulated, subcapsular nodule, measuring 1.1 cm in the largest dimension (Fig. 2). The surrounding liver parenchyma was not cirrhotic.

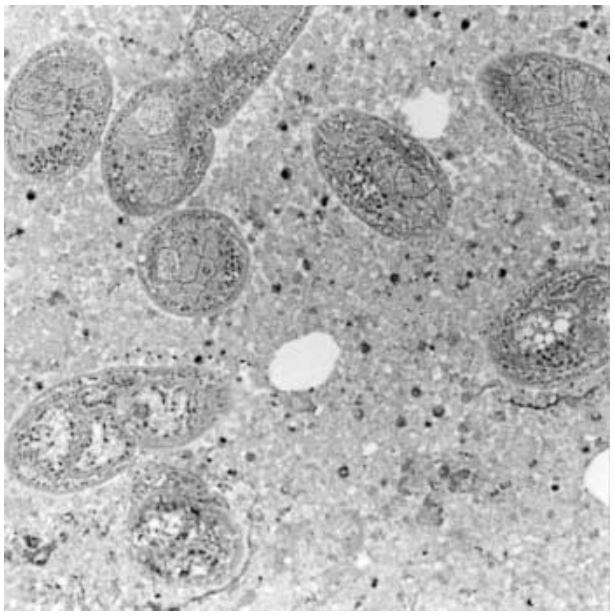

Fig. 4. Many transverse sections of a nematode in the coagulative necrosis of liver parenchyma (H&E, ×200).

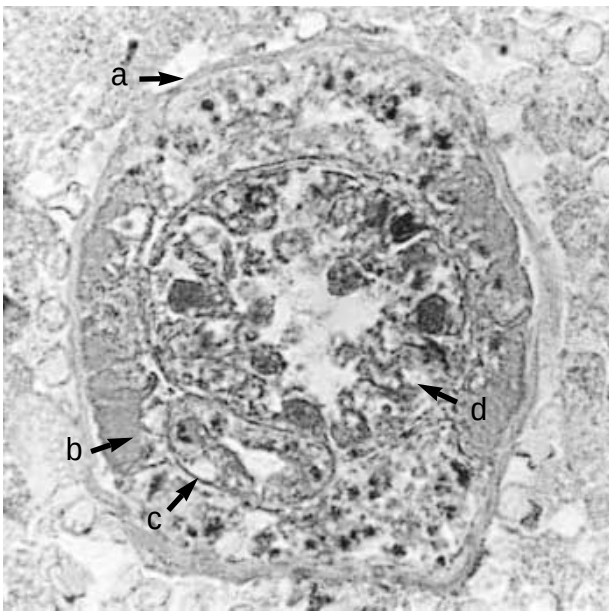

Fig. 5. The worm found in the liver. Cuticle (a), muscle (b), an intestine (c), and a reproductive tube (d) (H&E, ×400).

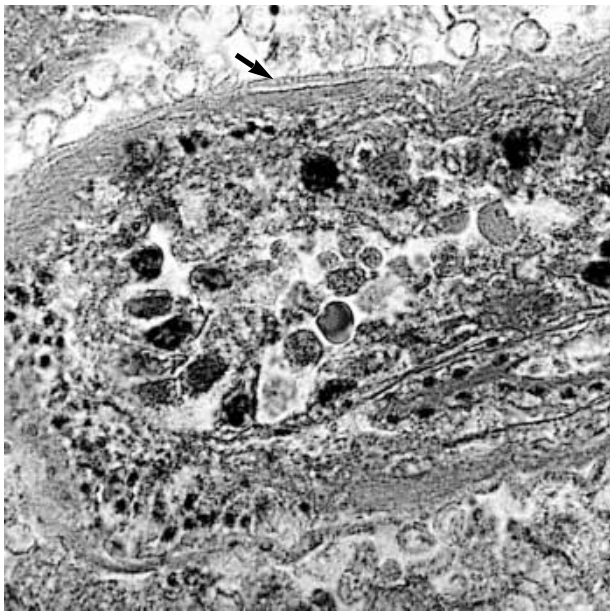

Fig. 6. Cuticle with fine transverse striations (arrow) of *Dirofilaria immitis*. Central portion of body cavity is filled with a reproductive tube. (H&E, ×600).

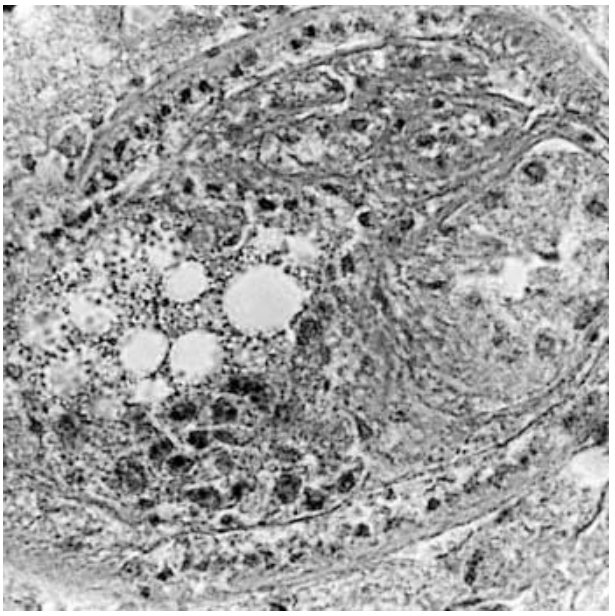

Fig. 7. Internal organs of *Dirofilaria immitis* undergone degenerative change. Partly preserved reproductive tube and well-developed muscle are noted (H&E, ×400).

Light microscopically, the lesion consisted of conglomerated oval to round necrotic areas, in which hepatocytes and eosinophils were undergone coagulative necrosis. There were many hexagonal or diamond-shaped Charcot-Leyden crystals in the necrotic areas. The necrotic regions were surrounded by inner granulomatous rim and outer zone of mixed inflammatory cell infiltrates containing plasma cells, lymphocytes, foreign body-type giant cells, and abundant eosinophils (Fig. 3). The adjacent hepatocytes showed regenerative changes, such as double nuclei, mild nuclear pleomorphism, and pale abundant cytoplasm. Fatty change of moderate degree was also evident. Bile ducts in portal areas were unremarkable.

In the necrotic area, there were up to 35 transverse or slightly longitudinal sections of a nematode, ranging 30-80 μm

in diameter and at least 2 cm in total length (Fig. 4). The nematode revealed considerable degenerative change and the internal organs were only partly preserved. In a relatively well-preserved section (Fig. 5), thin (1.5-5 μm) and multilayered cuticle with transverse striations (Fig. 6) surrounded polymyarian and muscle bundles, which occupied a sixth of each side of outer body cavity, interrupted by areas of degenerative changes where lateral chords should occupy (Fig. 7). Central portions of the body cavity were occupied by two tubular structures; one smaller intestine-like structure and the other presumed to be a single larger reproductive tube, most probably of male genital tube. There were neither shelled eggs nor microfilariae in and around the worm and necrotic areas. Based on the morphologic features of the worm, the nematode was diagnosed as immature male *Dirofilaria immitis*.

Supplementary diagnostic tests

Stool examination for helminths was negative. Intradermal tests for *P. westermani* and *C. sinensis* were non-reactive. Serum antibody tests for *Paragonimus westermani*, *Clonorchis sinensis*, *Toxocara canis* and *T. cati* were non-reactive when undertaken by western blot. Antibody tests by ELISA using crude extracts of adult filarial worms were available in Department of Medical Zoology, National Institute of Health (Seoul, Korea). Absorbance for *Brugia malayi* was 0.327 (positive control; 3.692) and for *Dirofilaria immitis* was 3.197 (positive control; 4.5), which supported the diagnosis of a nematode as a *D. immitis.*

The patient was discharged after operation without any complication. During 12 months of follow-up period, he has been in good health.

DISCUSSION

D. immitis infection is diagnosed by identifying the worm species in surgical or autopsy specimens. Mature *D. immitis* females are 25 to 30 cm by 1 to 2 mm, and mature males are 12 to 18 cm by 1 to 2 mm. Only immature worms of *D. immitis*, measuring up to 100 to 300 μm in diameter, have been found in human (2). The multilayered cuticle is 5 to 25 μm thick and projects inward at the lateral chords to form internal longitudinal ridges. The surface of the cuticle contains fine transverse striations 2 to 7 μm apart. The muscle is well developed and is usually projecting far into the body cavity. Internal organs consist of an intestine and two uteri in the female, and an intestine and a single reproductive tube in the male. Ova, spermatozoa, and microfilariae are not found in immature worms.

The morphologic features of the present worm including the absence of microfilariae, the multilayered cuticle with characteristic fine striations, well-developed muscle, poorly preserved lateral chords, and the internal organs consisting one intestine and a single reproductive tube were all compatible with those of immature male *D. immitis.*

Several other filarial nematodes could be differentiated based on the morphologic features. *Loa loa* have large diameter (about 600 μm), thin cuticle with irregularly spaced bosses, conspicuous lateral chords, and 3 or 4 uteri. The cuticle of *Onchocerca volculus* has characteristic annulations with regular spacing. *Dipetalonema perstans* and *D. streptocerca* have smooth surfaced cuticle and inconspicuous lateral chords. *Wuchereria bancrofti* and *Brugia malayi* could not easily differentiated on the light microscopic features, but they usually have thin and finely striated cuticle forming a low rounded ridge, rather than an internal longitudinal ridges and slight to moderately developed somatic muscle (2).

Out of helminths, other species may infest the liver to form a hepatic nodule, in which the possibilities of *Enterobius vermicularis, Ascaris lumbricoides, Strongyloides stercoralis, Toxocara canis, Capillaria hepatica, Clonorchis sinensis*, and *Fasciola hepatica* should be considered (10-12). The eggs are usually found in the granulomatous lesion in the cases of the schistosomiasis, hepatic capillariasis, fascioliasis, paragonimiasis, and ascariasis. In visceral larva migrans due to *Toxocara canis* or *T. cati*, there are a massive outpouring of eosinophils and often areas of central necrosis (10). Hepatic granulomas due to *Strongyloides stercoralis* and *Enterobius vermicularis* were also reported (11, 12). The absence of eggs or massive outpouring of eosinophils in this case contributed to rule out the other helminths as well as the morphologic features of a nematode.

The present case is the third case of human dirofilariasis reported in Korea. The first case was a 33-yr-old woman with abdominal *Dirofilaria (Nochtiella)* species infection in 1976 (7). She had lived in Thailand and Sri Lanka for 5 yr prior to the diagnosis. The second case was a pulmonary dirofilariasis in a 47-yr-old man presenting with left chest pain for 1 month (13). In human pulmonary dirofilariasis, over 50% of patients were asymptomatic and their lesions were usually discovered as "coin lesions" in routine roentgenograms of the chest. The most common clinical symptoms are chest pain, cough, and hemoptysis (2, 5). Considering the high infection rate (28.3%) of German shepherds in Korea (14), the relative rarity of reported human dirofilariasis among Korean may be partly due to under-evaluation of a small solitary pulmonary nodule, which is frequently thought to be a tuberculous nodule.

There is no confirmative diagnostic method of *D. immitis* but identifying the worm in surgical specimens. In combination with surgical removal, serum antibody tests for various nematodes using western blot or ELISA can be used to get a supportive evidence of parasitic infection.

The present case is the first one of hepatic dirofilariasis in human, whereas a few hepatic dirofilariasis in dogs have been reported. Although *Dirofilaria* species only rarely involve the liver in human, the possibility should be considered in the differential diagnosis of benign hepatic nodule.

REFERENCES

1. Muro A, Cenchi C, Cordero M, Simon F. *Human dirofilariasis in the European Union. Parasitol Today 1999; 15: 386-9.*
2. Neafie RC, Connor DH, Meyers WM. *Dirofilariasis. In: Binford CH, Connor DH, editors, Pathology of tropical and extraordinary diseases. vol 2, Washington DC: AFIP, 1976: 391-6.*
3. Chapman BL, Hendrick MJ, Washabau RJ. *Granulomatous hepatitis in dogs: nine cases (1987-1990). J Am Vet Med Assoc 1993; 203: 680-4.*
4. Goggin JM, Biller DS, Bost CM, DeBey BM, Ludlow CI. *Ultrasonographic identification of Dirofilaria immitis in the aorta and liver of a dog. J Am Vet Med Assoc 1997; 210: 1635-7.*
5. Mrugeshkumar K, Shah BS. *Human pulmonary dirofilariasis: Review of the literature. South Med J 1999; 92: 276-9.*
6. Takeuchi T, Asami K, Kobayachi S, Masuda M, Tanabe M, Miura S, Asakawa M, Murai T. *Dirofilaria immitis infection in man: Report of a case of the infection in heart and inferior vena cava from Japan. Am J Trop Med Hyg 1981; 30: 966-9.*
7. Rim HJ. *A case of human infection with Dirofilaria (Nochtiella) species. Korean J Parasitol 1976; 14: 164.*
8. Tada I, Sakabuchi Y, Eto K. *Dirofilaria in the abdominal cavity of a man in Japan. Am J Trop Med Hyg 1979; 28: 988-90.*
9. Theis JH, Gilson A, Simon GE, Bradshaw B, Clark D. *Case report: unusual location of Dirofilaria immitis in a 28-year-old man necessitates orchiectomy. Am J Trop Med Hyg 2001; 64: 317-22.*
10. Goodman ZD, Ishak KG. *Medical diseases of the liver. In: Silverberg SG, DeLellis RA, Frable WJ, editors, Princicles and practice of surgical pathology and cytopathology. Vol 2, 3rd ed, New York: Churchill Livingstone, 1997: 1919-24.*
11. Mondou EN, Gnepp DR. *Hepatic granuloma resulting from Enterobius vermicularis. Am J Clin Pathol 1989; 91: 97-100.*
12. Poltera AA, Katsimbura N. *Granulomatous hepatitis due to Strongyloides stercoralis. J Pathol 1974; 113: 241-6.*
13. Lee KJ, Park GM, Yong TS, Im J, Jung SH, Jeong NY, Lee WY, Yong SJ, Shin KC. *The first Korean case of human pulmonary dirofilariasis. Yonsei Med J 2000; 41: 285-8.*
14. Lee JC, Lee CY, Shin SS, Lee CG. *A survey of canine heartworm infections among German shepherds in South Korea. Korean J Parasitol 1996; 34: 225-31.*