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## HUMAN FOCAL NODULAR HYPERPLASIA-LIKE LESION IN THE LIVER OF A CAT

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### SUMMARY

A young cat clinically displaying marked ascites had multiple nodular hyperplasia in the liver. One of the nodules sampled at exploratory laparotomy was studied histopathologically. The nodule consisted mainly of hyperplastic hepatocytes with a central stellate scarlike connective tissue. The connective tissue had thick-walled blood vessels and radiating bands of fibrous connective tissue extending peripherally, dividing the nodule into pseudoblobules. The lesions resembled focal nodular hyperplasia (FNH) in man. Serial section revealed a single large artery with the splitting of the internal elastic lamina running into the central connective tissue and branching to connect with the main vessels. The arterial branchings formed a spider-like structure. From these findings, it was suggested that the nodule had developed from a hepatic response to pre-existing vascular anomalies as had been reported in human FNH.

Hepatic nodular hyperplasia occurs commonly in old dogs, but it is rare in other domestic animals (14). In mice (6) and rats (16), such nodules are generally believed to be early stages in the formation of larger neoplasms. There has been no report of this lesion in cats. This report describes the histological findings of hepatic nodular hyperplasia in a cat.

A female Persian cat, 2 years old, showed constipation and abdominal distention with ascites. There was no history of hormonal treatment. The ascitic fluid, watery, clear and strawcolored, was aspirated 5 times over 2 months, for a total amount of 3.5 l. The aspirate revealed the following findings; negative Rivalta reaction, 2.4 % protein concentration, 98.0 mg glucose/100 ml, and a few erythrocytes, white blood cells and unidentifiable round cells in the sediment. Heart function was normal 40

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days after the cat had begun to show clinical ascites. By then the removed ascitic fluid totalled about 1.2 l in volume. The serum total protein was 6.0 g/100 ml, albumin 2.17 g/100 ml and A/G ratio 0.57. Exploratory laparotomy was performed 11 days after ascitic fluid was last removed. The splenic capsule was found to be severely thickened with fibrous tissue, and nodules about 7 mm in diameter, were scattered on the visceral surface of the liver. One of the hepatic nodules was excised with the surgical removal of the spleen. They were fixed in 10% formalin for pathological examination. The cat died the day after the operation.

The formalin-fixed liver nodule was firm in consistency and thinly encapsulated. On cross section, the nodule appeared to be yellowish white and partially gray in color, and had fibrous tissue in the central area.

Histologically, the nodule consisted of hyperplastic hepatocytes with a stellate scarlike connective tissue in the central portion (Figs. 1 and 3), associated with a single large artery in the peripheral area (Fig. 4). The connective tissue was seen in 3 independent parts on the largest cross section, but serial sections demonstrated that they were interconnected. The nodule had no central veins or portal triads. The stellate connective tissue had a myxomatous background, and contained proliferating small pseudoductules, occasionally with bile stasis, and many blood vessels (Figs. 5 and 6). The connective tissue radiated peripherally, frequently with small vessels, dividing the nodule into pseudolobules (Fig. 3). In some parts of the connective tissue there were a number of dilated vessels with thin wall and empty lumen, which formed a network structure suggestive of lymphatic vessels (Fig. 3). Some hemosiderin-laden macrophages and small aggregates of lymphocytes were present in the connective tissue. In some parts around the stellate connective tissue, micronodules of hepatocytes seemed to have formed with small vessels as the center. Focal proliferation of bile ducts, sometimes with bile stasis, were scattered at the periphery of the nodule with occasional lymphocytic infiltration. The peripheral sinusoids were moderately filled with blood, some being dilated as in telangiectasis. The dilated vessels with thin collagen walls, resembling central veins, were often seen in the subcapsular areas. Some myeloid cells were seen in the sinusoids.

The hyperplastic hepatocytes showed almost the same structure as the normal hepatic cells though some exhibited hydropic degeneration. The cellular arrangement was somewhat different from normal. Hepatocytes were arranged in irregular cords showing cell plates of varying thickness (Fig. 2), with intervening narrowed sinusoids or reticulum fibers. The cytoplasm of almost all the hepatocytes stained positively with PAS, though those in areas adjacent to the scarlike connective tissue were PAS-negative. The hepatocytes within the nodule revealed no hyperbasophilia with toluidine blue stain.

In addition, vascular anomalies were noted in the nodule; marked thickening of blood vessels in the stellate connective tissue and a single large artery in the area

where the nodule was attached to the liver. The internal elastic lamina of this artery was split and thickened due to fibromuscular proliferation between the elastic fibers (Fig. 4). The serial sections demonstrated that this artery ran into the center of the nodule, and branched to connect with the main vessels in the connective tissue (Fig. 7). This branching formed an arterial spider-like structure. The nodule appeared to be supplied by this artery only. The arterial inside diameter was 750  $\mu\text{m}$ . In our experience, in the normal adult cat, the maximum inside diameter of proper hepatic artery was 682  $\mu\text{m}$ , the mean of 15 proper hepatic arterial branches was 180  $\mu\text{m}$ , and the inside diameter of the smaller branches including the interlobular arteries was less than 73  $\mu\text{m}$ . The marked thickening of the branched arterial walls resulted from fibromuscular proliferation and mucoid degeneration in the media, and from endothelial swelling (Fig. 6). Some walls had mild focal hemorrhage or infiltration of inflammatory cells. Occasionally the thickening caused the complete occlusion of the smaller branches. The internal elastic lamina was lost in all of the arterial branches. A larger vessel which could not be recognized as a branch of the artery was seen, but this vessel had no elastic lamina.

The spleen was congested atrophic and firm with severe fibrous thickening of the capsule. Histologically it showed marked thickening of the capsule and trabeculae with additional fibrous strands, congestion, and follicular hyperplasia.

The hepatocellular hyperplastic nodule in this case was characterized by the central scarlike connective tissue and the vascular anomalies. It is known that hepatic hyperplastic nodules in old dogs have no fibrous stroma (14). Hepatocellular neoplasms of mice are classified into two types; adenoma, synonymous with benign hepatoma or hyperplastic nodule and carcinoma (6). The nodular growths are considered to be early stages in the formation of larger adenomas or carcinomas. In rats the nodules, consisting of hyperplastic hepatocytes generally lacking in cytological alteration and surrounded by fibrous trabeculae, have been classified as regenerative (16), apart from neoplastic nodules in mice. Spontaneous hyperplastic nodules with fibrosis, forming such pseudolobules as seen in cirrhotic liver, are observed in the liver of slaughtered swine (7). In the hepatic nodules of dogs, mice, rats, and swine, however, lesions such as the central stellate scarlike tissue, intranodular proliferation of bile ducts and vascular abnormalities, have not been described.

In human medicine, focal nodular hyperplasia (FNH) in the liver is defined by the histological characteristic that a stellate mass of connective tissue in the center extends radially towards the periphery (4), and is also known as focal cirrhosis (2), or isolated nodule of regenerative hyperplasia (1). FNH lacks the normal lobular architecture and has an intranodular proliferation of bile ducts, by which it is distinguished from cirrhosis (10). FNH is generally single, but occasionally multiple (5,10,17). In addition, the vessels embedded within the scar frequently show extensive mucoid degeneration of the medial layer, thickened walls and fragmentation and

splitting of elastic fibers (5,17). On the other hand, intrahepatic vascular anomalies are reported in arterio-venous fistula (3) and hepatic vascular hamartoma (12) of dogs. However, no regenerative hepatocyte hyperplasia is associated with these disorders. As described above, the present lesions closely resembled FNH in man, but the entity of FNH in animals is not defined. Therefore, this case was diagnosed as human focal nodular hyperplasia-like lesion in the liver of a cat.

FNH occurs mostly in females of child bearing age, generally without clinical symptoms, and is found incidentally at laparotomy for other diseases (5, 10), although portal hypertension has been reported in a few cases with multiple nodules (9). Marked ascites and atrophic fibrous spleen probably suggests severe portal hypertension in this case.

The pathogenesis of FNH has been controversial. This lesion has been variously considered as a neoplasm (8), a hamartoma (13,15), a response to either ischemia or focal injury (1, 2, 18), or as being induced by oral contraceptives (11). WHELAN et al. (18) have, on arteriographic evidence, suggested that FNH results from anomalous blood supply. WANLESS et al. (17) have observed by morphometric analysis that an anomalously large artery was present in FNH, that it branched to form an arterial spider-like structure, and that each terminal arterial branch supplied a separate micronodule, 1 mm in diameter. In other words, adjacent micronodules coalesced to form the FNH. From these findings, they proposed the theory that FNH is a hyperplastic response of the hepatic parenchyma to a pre-existing arterial spider-like malformation. They also speculated that vascular and neuroendocrine anomalies are developmental in origin, as FNH frequently coexists with the anomalies. In the present case, it is noteworthy that central scarlike tissue was formed, accompanied by the larger branches of the single artery. This artery had unusual size and branchings, and a part of the nodule seemed to consist of a cluster of micronodules. These may support the idea that the present nodules were developed as a response to pre-existing vascular anomalies. The recognition of human FNH-like lesion in a cat may present the potential benefits of experimental studies on FNH using cats.

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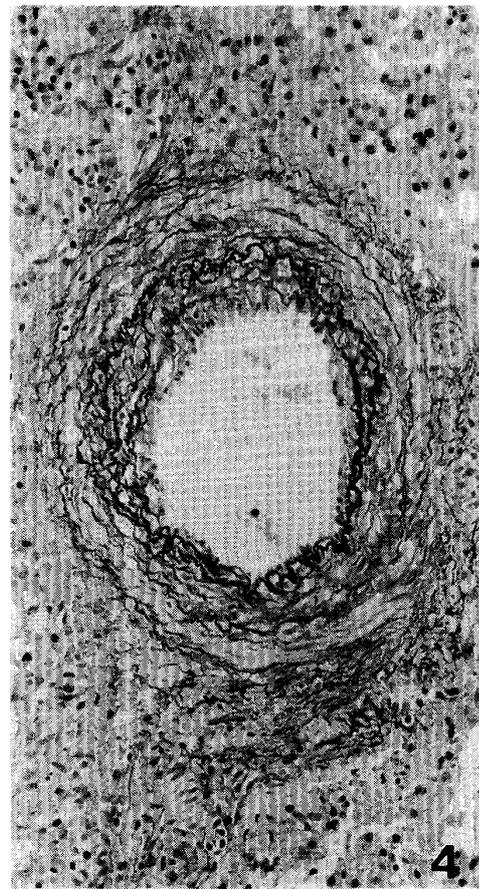
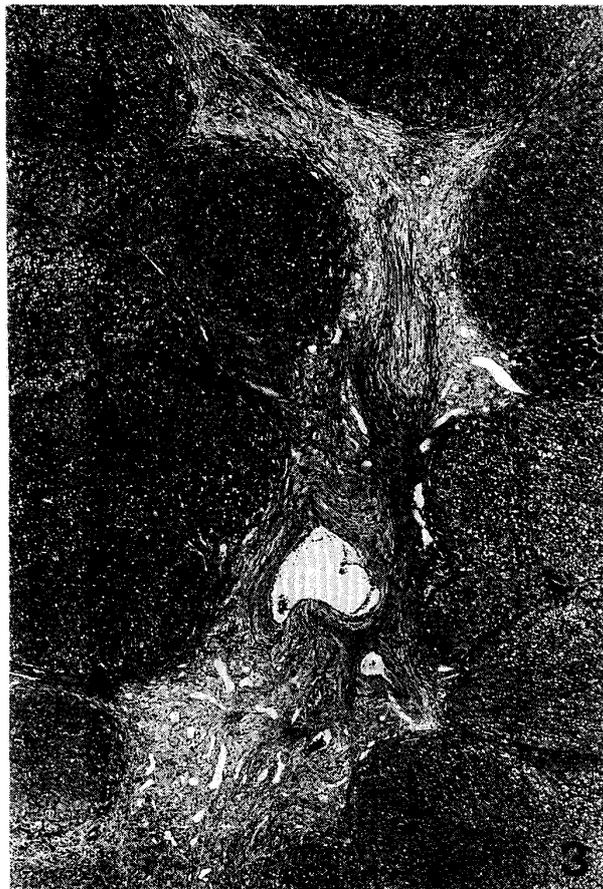
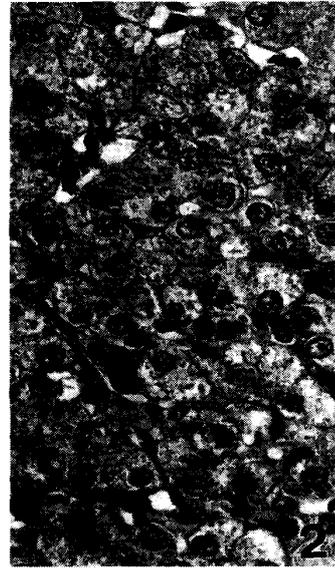
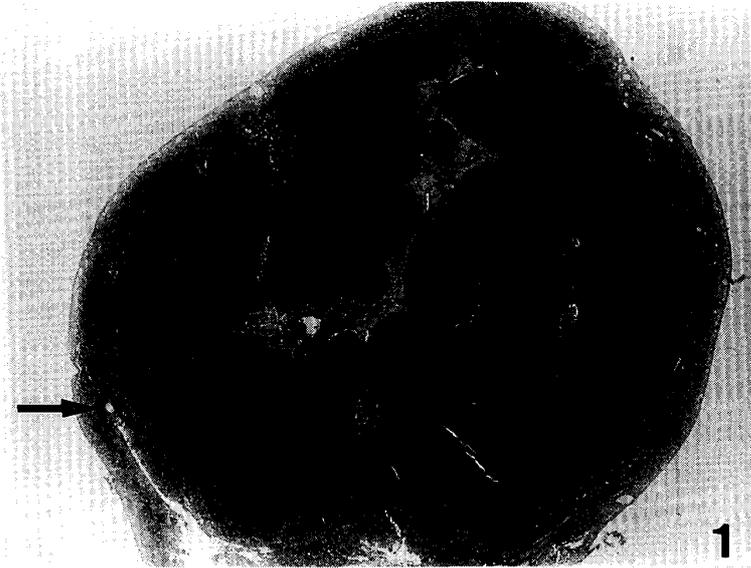
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## EXPLANATION OF PLATES

## PLATE I

- Fig. 1 Section of the hepatic nodule. There are hyperplastic hepatocytes with central stellate scarlike connective tissue having radiating bands. Note the single large artery (arrow). The lower part is the area where the nodule is attached to the liver. Hematoxylin and eosin (HE) stain.  $\times 8$ .
- Fig. 2 Higher magnification of hyperplastic hepatocytes. The cells show almost the same structure as the normal hepatic cells, but they arrange in irregular cords. HE stain.  $\times 480$ .
- Fig. 3 Higher magnification of the central stellate scarlike connective tissue in Fig. 1. There are thick-walled blood vessels and lymphatic-like vessels. The liver parenchyma is divided into pseudolobules by radiating fibrous bands from the central connective tissue. HE stain.  $\times 40$ .
- Fig. 4 A single large artery in the connective tissue. Splitting of the internal elastic lamina and subintimal fibro-muscular proliferation can be seen. Weigert stain.  $\times 200$ .



## PLATE II

- Fig. 5 Focus of pseudoductular proliferation in the central stellate scarlike tissue with myxomatous background. Bile stasis (arrow) is occasionally seen. HE stain.  $\times 400$ .
- Fig. 6 Arteries in the central stellate scarlike tissue. Branched arterial walls are thickened due to fibromuscular proliferation and mucoïd degeneration in the media. HE stain.  $\times 400$ .
- Fig. 7a-c Serial sections of a part of a hepatic nodule. Note the single large artery (arrows). This artery runs into the nodule and connects with the main vessels in the central scarlike connective tissue. HE stain.  $\times 13$ .

