

# HEPATOCELLULAR ADENOMA AND FOCAL NODULAR HYPERPLASIA OF THE LIVER: DIFFERENTIAL DIAGNOSIS IN DOGS

JOSÉ GUILHERME XAVIER

Graduate student

Faculdade de Medicina Veterinária e Zootecnia da USP

MARIA LUCIA ZAIDAN DAGLI

DVM

Faculdade de Medicina Veterinária e Zootecnia da USP

MARIA REGINA VIANNA

DM

Hospital das Clínicas - USP

BENJAMIN EURICO MALUCELLI

Associate Professor

Faculdade de Medicina Veterinária e Zootecnia da USP

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**SUMMARY:** Among the hepatic lesions routinely found in veterinary necropsy practice, nodular lesions are the less described. These lesions include both reactive or neoplastic processes and hamartomas. This study was performed in order to differentiate the hepatocellular adenomas (HA) from the hepatic focal nodular hyperplasia (FNH) in dogs. Ten cases of nodular hepatic lesions in dogs were surveyed from the archives of the Department of Pathology of the "Faculdade de Medicina Veterinária e Zootecnia da Universidade de São Paulo". To each case, histochemical and immunohistochemical methods were applied in order to characterize the lesions, according to histological human predefined criteria. From the results recorded it was possible to diagnose eight cases of FNH and two cases of HA. It was concluded that these techniques can be easily performed and are suitable for the proposed objectives.

**UNITERMS:** Neoplasms of dogs; Liver neoplasms; Liver diseases of dogs; Diagnosis, differential

## INTRODUCTION

Primary hepatobiliary tumors are relatively uncommon in small animals<sup>6</sup> but they are considered by some the most common visceral neoplasm in dogs, excepting the lymphomas<sup>3</sup>.

Among the various types of primary liver neoplasms, the hepatocellular adenomas, hepatocellular carcinomas and bile duct carcinomas are the most frequent in small animals<sup>7</sup>. Benign tumors are reported to be less common than malignant ones<sup>9</sup>. Little information is available about the behavior and histological characterization of hepatocellular adenomas (HA) and focal nodular hyperplasia (FNH) of the liver of dogs.

These lesions are quite similar. Grossly, HA appears as friable, well circumscribed, highly vascular masses, usually single. They often exhibit a pedunculated attachment, and occur with higher frequency in dogs over 10 years of age<sup>5</sup>. They can be sometimes surrounded by a connective tissue capsule<sup>3</sup>. FNH has been presented as grossly visible softer or firmer, single or multiple parenchymal nodules in the liver, that occur naturally in 15% to 60% of old dogs<sup>2</sup>, accompanying fibrotic, congestive or degenerative processes.

Histologically, HA may be difficult to distinguish from FNH, or even from normal liver tissue<sup>6,7</sup>. Nevertheless, no reports in veterinary pathology describing the differential histological characteristics of these two lesions in dogs were found.

In human medical literature, hepatic nodular lesions can be classified as either HA or FNH according to some histological criteria<sup>4</sup>. HA on histological examination is a monotonous regular proliferation of hepatocytes, in general not arranged in typical cords, separated by normal or dilated sinusoids, and is characteristically devoid of bile ducts<sup>4</sup>. FNH consists of a proliferation of normal hepatocytes, containing stellate fibrous central scar, being prominent the presence of intra-nodular biliary ducts<sup>8</sup>.

This study was performed in order to distinguish these two lesions in dogs, applying the same human histological criteria.

## MATERIAL AND METHOD

Necropsy and biopsy records (from 1936 to 1987) of the Department of Pathology of the "Faculdade de Medicina Veterinária e Zootecnia da Universidade de São Paulo" were reviewed for the occurrence of nodular hepatic lesions in dogs. Ten cases were found that have been diagnosed as hepatocellular adenomas, and that kept available slides and/or paraffin blocks.

All the liver specimens were fixed in 10% formalin and routinely embedded in paraffin. About 5 µm thick sections were obtained and stained with the following methods: hematoxylin-eosin, Masson's trichrome and Perls (Prussian blue) for iron. In nine cases an immunohistochemical method (immunoperoxidase) was applied to detect low-and-high molecular weight cytokeratin (DAKO Corporation-USA), to evidentiate the presence of biliary ducts within the lesions. All the cases were analysed for the following histological variables: sharp demarcation, fibrous septation, vacuolar degeneration, ductal proliferation, portal triads, presence of bile ducts, hemosiderin, peliosis and abnormal vessels.

## RESULTS

Tab. 1 shows the characteristics observed in the collected ten cases.

Only one of the cases showed sharp demarcation. Two of them, which were diagnosed as FNH, presented a fibrous septation within the lesions; detected by Masson staining method for collagen fibers.

Most of the cases of FNH (eight in ten) showed vacuolar degeneration in the hepatocytes, with different patterns of lipid droplets accumulation in the cytoplasm of the cells.

Six among eight cases diagnosed as FNH presented some degree of biliary ducts proliferation. There were not portal triads within or in the periphery of the lesions diagnosed as HA. These findings were confirmed by immunoperoxidase which was negative for epithelial structures (biliary ducts) in HA cases.

In four cases diagnosed as FNH biliary ducts were present, confirmed by immunoperoxidase (Fig. 1). In three cases, the results were inconclusive because the materials were not properly preserved and in one case there was no epithelial structure positively marked by the monoclonal antibodies. Besides this, the case was diagnosed as FNH because of the arrangement of hepatocytes and the presence of other portal structures in the center of the lesion.

The presence of hemosiderin was detected both in adenoma and FNH cases. The two adenoma cases showed peliosis (dilated blood vessels) and abnormal blood vessels (thickened walls and dilated lumen) (Fig. 3), that could also be seen in some FNH cases.

About the arrangement of the hepatocytes, FNH lesions in general kept the normal hepatic structure (Fig. 2), while HA cases showed different patterns of organization, with a tendency to form acini (Fig. 3).

## DISCUSSION

As mentioned by COTCHIN<sup>1</sup> (1984), the aim of the study of neoplasms and correlated diseases in domesticated animals should be the maintenance of their welfare. In this line of thought, it can be said that the differential diagnosis between FNH and HA is important in veterinary practice, as in human pathology, for many reasons.

The methods presented here, commonly used in human pathology, brought satisfactory results, and may be considered suitable for the proposed objectives. They are accessible and can be easily performed.

In one case diagnosed as FNH there were no detectable bile ducts, perhaps because the smaller lesions do not always contain these structures, as mentioned by some<sup>3</sup>.

Anyway, our results have shown that histopathological examination of the liver focusing tissular architecture and cellular characteristics by using only common histochemical staining methods allows the establishment of the diagnosis, rendering dispensable the use of the immunohistochemical method.

Benign epithelial liver tumors can be only incidental findings at laparotomy and necropsy<sup>9</sup>, but they are also detected in veterinary medical care, claiming for a previous knowledge of diagnostic, evolutive and therapeutic characteristics.

Surgical biopsies are indicated, followed by histopathological examination of the specimens, considering the above mentioned differential criteria.

Because of its highly vascular stroma, HA can disrupt and cause hemoperitoneum<sup>6</sup> provoking the sudden death of the animal. Human patients are reported to experience abdominal pain and an acute onset of symptoms due to tumor bleeding or rupture<sup>4</sup>. This characteristic is rarely observed in human cases of FNH.

FNH has variously been considered a neoplasm, hamartoma, or a reaction to focal injury. In a study, the authors considered these lesions a hyperplastic response of the liver parenchyma to the presence of preexisting vascular formation<sup>10</sup>. Due to the paucity of recorded data, in our study it was impossible to correlate the histopathological diagnoses with the clinical cases.

Lastly, contrary to the literature data<sup>2,4,6,7</sup>, our study has shown that it is possible to differentiate FNH from HA in dog's liver.

We suggest that other studies combining clinical, semiological and histopathological data should be encouraged in order to better understand the behavior of these lesions in animals.

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XAVIER, J.G.; DAGLI, M.L.Z.; VIANNA, M.R.; MALUCELLI, B.E. Adenoma hepatocelular e hiperplasia nodular focal do fígado: diagnóstico diferencial em cães. *Braz. J. vet. Res. anim. Sci.*, São Paulo, v.29, n.1, p.77-82, 1992.

**RESUMO:** Dentre as alterações hepáticas encontradas na rotina de necrópsias em medicina veterinária, as lesões nodulares são as menos caracterizadas. Estas incluem processos reacionais ou hiperplásicos, neoplásicos e hamartomas. Este estudo foi realizado com a finalidade de diferenciar os adenomas hepatocelulares (AH) das hiperplasias nodulares focais (HNF) do fígado em cães. Dez casos de lesões nodulares hepáticas em cães foram levantados dos arquivos do Departamento de Patologia da Faculdade de Medicina Veterinária e Zootecnia da Universidade de São Paulo. Métodos histoquímicos e imunohistoquímicos foram aplicados a cada caso, com a finalidade de caracterizar as lesões, de acordo com critérios histológicos definidos para as mesmas lesões no homem. Dos resultados descritos foi possível diagnosticar oito casos de HNF e dois casos de AH. Conclui-se que estas técnicas podem ser facilmente utilizadas e que são adequadas para os objetivos propostos.

**UNITERMOS:** Neoplasias, cães; Neoplasias, fígado; Fígado, doenças, cães; Diagnóstico diferencial

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TABLE 1 - Histopathological findings in FNH and HA cases in dogs. São Paulo, 1989.

CASE	1	2	3	4	5	6	7	8	9	10
Sharp demarcation	-	-	-	-	-	-	+	-	-	-
Fibrous septation	-	-	-	-	-	+	+	-	-	-
Vacuolar degeneration	+	+	+	+	+	-	+	+	-	+
Ductal proliferation	-	-	+	+	+	-	+	+	+	-
Portal triads										
Central	-	-	+	+	+	+	+	+	+	+
Periphery	-	+	+	+	+	+	+	+	+	+
Bile ducts	+	-	+	+	inconcl.	+	+	inconcl.	inconcl.	-
Siderosis	+	-	+	-	-	-	-	+	+	+
Peliosis	+	+	-	-	-	+	-	+	+	-
Abnormal vessels	+	+	-	-	-	-	-	-	+	+
DIAGNOSIS	HA	HA	FNH	FNH	FNH	FNH	FNH	FNH	FNH	FNH

inconcl. = inconclusive

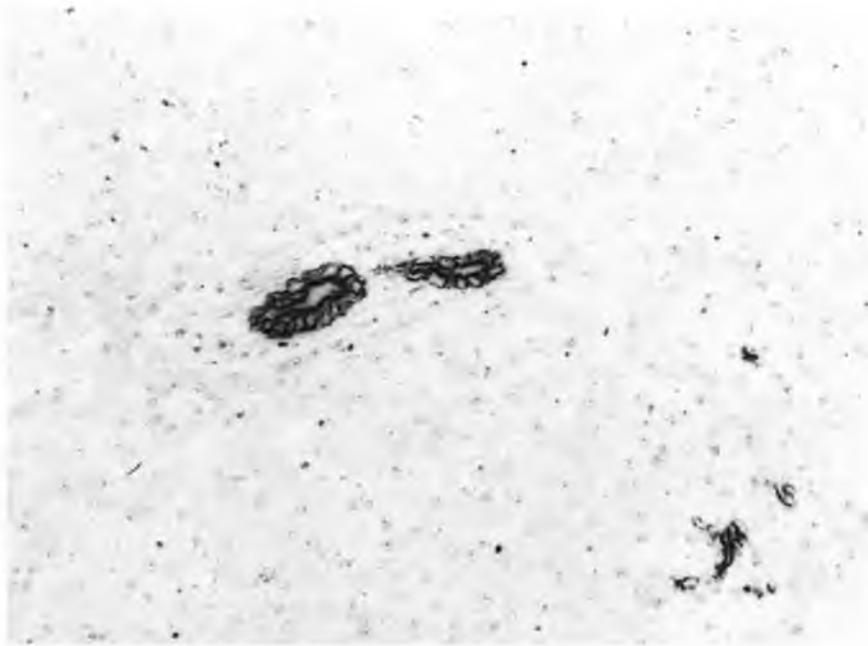


FIGURE 1 — Histological appearance of biliary ducts positively stained with immunoperoxidase in a FNH case (165x).

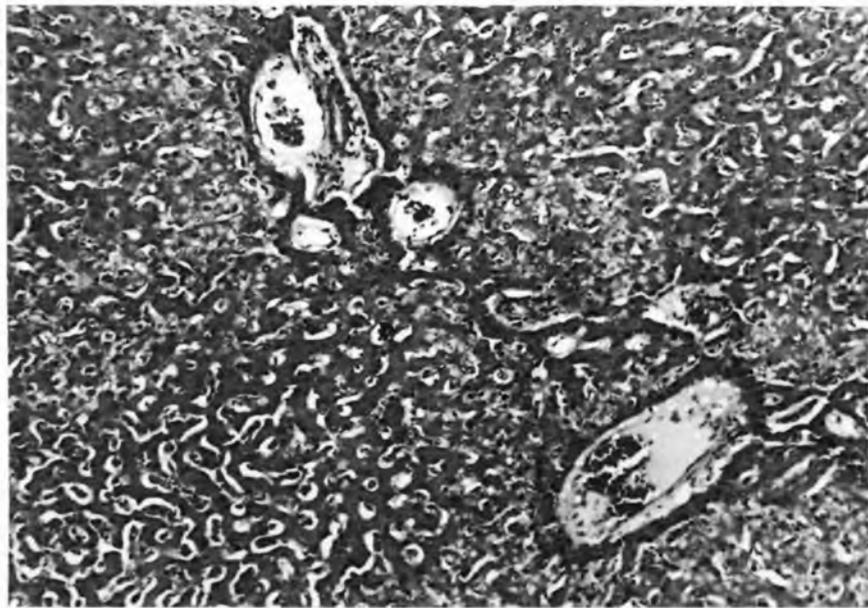


FIGURE 2 — Histological aspect of the central region of a FNH case. Disorganization of hepatocyte plates, vacuolar degeneration and portal triads (H.E. 165x).

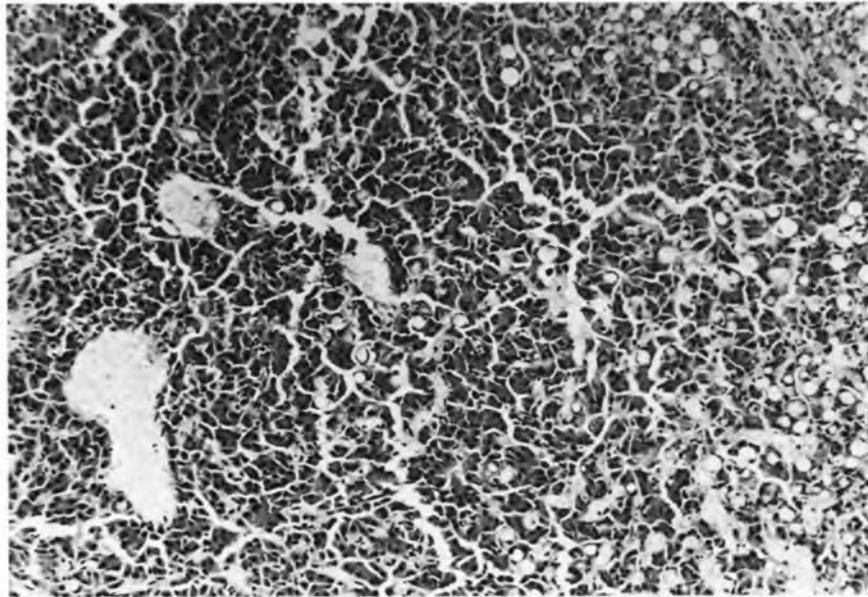


FIGURE 3 — An HA case, showing the disruption of hepatocyte plates, with a tendency to form acini, vacuolar degeneration and sinusial dilation (peliosis) (H.E. 165x).