Hepatic fatty cirrhosis in ruminants from western Texas

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For at least 60 years, a disease known as hard yellow liver has been diagnosed in sheep and cattle in western Texas. Since its first description in 1931,1 veterinary scientists have sought to discover the cause of the disease; however, the specific cause of hard yellow liver disease, or hepatic fatty cirrhosis (HFC), as it was later named, remains unknown. It is a sporadic disease, and no effective predictors of when the disease will develop have been discerned. Consequently, HFC remains a barrier to ruminant food animal production in western Texas.

In the past decade, research efforts have been frustrated and slowed because HFC has not been reproduced experimentally. In this review, we offer the current epizootiologic and clinical features of HFC.

Historical Features

Hepatic fatty cirrhosis was first observed in sheep and later in cattle in Reagan County, Texas in September 1931 (Fig 1).1 In 1930, yellow livers, described as carotenosis,2 were discovered in a group of cattle at the Illinois stockyards in Chicago. Interestingly, these same cattle were believed to originate from the southwestern part of the United States. The morphologic changes in livers and hepatic lymph nodes from the cattle in the Illinois stock yards and cattle from Texas with HFC were similar.

In 1932, Texas Agricultural Experiment Station scientists began experimenting with HFC. They found that cases of HFC were centered around Stiles, Texas in Reagan County, covering about a 500 km² area.3 For the next 37 years, experiment station scientists explored the possibilities of infective and toxic agents causing HFC. Transmission studies, using sheep liver and feeding trials with over 120 species of native plants, failed to identify a cause for the disease.4

In the mid to late 1960s, an extensive patho-

logic study of an episode of HFC in sheep was conducted.5 The primary feature of HFC was found to be a gradual fatty infiltration of the liver, progressing to cirrhosis over 8 to 10 months. The lesions began in parenchyma along the hilar vessels on the visceral surface and spread peripherally to involve up to 80% of the liver (Fig 2). Histologically, HFC is manifested as an accumulation of intracytoplasmic fat in hepatocytes around the central veins. Lipid accumulation continues with the formation of fatty cysts that eventually rupture and allow for the development of bridging fibrosis. The conclusion of that study was speculation that HFC represented a chronic hepatotoxosis associated with the ingestion of an antilipotropic toxin. It was hypothesized that such a compound would block synthesis and secretion of lipoproteins by the liver, resulting in progressive fatty liver and terminating in cirrhosis.

Figure 1—Map of Texas counties, showing known geographic areas where hepatic fatty cirrhosis (HFC) has been diagnosed. (1) Area in western Texas around Reagan County; (2) area in southern Texas around Dimmit and La salle Counties.

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Major episodes of HFC developed again in sheep during the winter months of 1969 to 1970 and 1976 to 1977. It was following the latter episode that studies into the eating habits of sheep were conducted in an attempt to characterize the forage diets of sheep at times when HFC developed vs the times when it did not. Although changes were observed in the dietary intake of grasses and forbs during these periods, it also was discovered that fungi were abundant on the native vegetation and in fecal samples of sheep during the years 1976 and 1977.

In 1974 and 1975, HFC was documented in white-tailed deer in Dimmit and LaSalle Counties of southern Texas (Fig 1). This was the first time that HFC had been detected in ruminants outside the original 5-county zone in western Texas around Stiles. Continuously, from 1969 through 1976, white-tailed deer in southern Texas were determined to be affected with HFC.

In 1978, samples of fungus-infected grasses were determined to be contaminated with Phomopsis leptostromiformis. Initial attempts to reproduce HFC with the fungus were conducted by feeding whole cultures to adult ewes. This resulted in acute hemorrhagic abomasitis terminating in death within 24 hours.

In the early 1980s, work was begun on the isolation and identification of toxins associated with the fungus. A mycotoxin identified as toridin A was purified from cultured P. leptostromiformis and was found toxic to mice. It also induced acute hemorrhagic gastritis. Long-term feeding studies with lower doses were not conducted with P. leptostromiformis cultures or with the purified toxin.

**Epizootiologic Features**

The primary geographic area where HFC is known to develop in ruminants consists of sandy to silty, clay loam soils and is classified as a semiarid grassland. Mean annual precipitation is from 35 to 40 cm and is concentrated in the periods of April and May, and September and October.

During the years 1931, 1937, 1941, 1961, 1965, 1977, and 1987, when there were severe episodes of HFC, rainfall patterns varied. There was above average rainfall in August and September, followed by an unusually wet winter (ie, January and February). The spring rains normally seen in April and May were less than average, and typically, the summers were dry. This resulted in a bloom of available vegetation February through May. Moreover, the vegetation was heavily infected with a fungus. Because of the excessively dry succeeding weather, available summer vegetation was less than average (Fig 3).

**Clinical Features**

Hepatic fatty cirrhosis appears to affect only ruminants. The disease has been observed in sheep, cattle, goats, white-tailed deer, and pronghorn antelope. Rabbits, coyotes, turkeys, quail, horses, and wild hogs from a ranch in western Texas where HFC was diagnosed in 1965 and 1966 were necropsied and checked for HFC; however, evidence of the disease was not found in any.

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of these animal species, and it is presumed that monogastric animals are not susceptible to HFC. The disease is not restricted to any sex, breed, or age of animal. However, in young growing animals, the disease appears to develop more quickly and with greater severity, as determined by the earlier appearance of signs and the more advanced development of lesions in lambs, compared with adult sheep. Affected lambs sent to feedlots usually make poor weight gains and die in hepatic coma. Characteristic lesions of HFC have been observed in slaughtered lambs as early as August following the spring in which they were born. The shortest period between encounter with the assumed etiologic agent and the first clinical signs seems to be from 6 to 8 months.

The first recognizable sign of HFC is a failure to gain or maintain weight. Even when supplemental feed is provided, affected animals do not gain weight. As the hepatic lesions progress, animals become emaciated, and the hair coat or fleece has a rough appearance. The affected animal may stand with an arched back with its head down. In sheep, there is ascites and loss of wool crimp as the disease progresses. Manifestations of CNS derangements, such as signs of depression, pressing of the head against solid objects, and walking with the head held high and tilted, may be observed. In the more terminal stages of advanced hepatic disease, the sheep become immobile and die, usually in a state of hepatic coma. Icterus seldom develops in HFC. Rectal temperature remains within normal limits, except in the terminal stages of the disease, when it becomes subnormal.

Sheep affected with severe HFC are typically anemic, as indicated by low PCV and blood hemoglobin concentrations. Conjugated and unconjugated serum bilirubin concentrations are not altered appreciably as the severity of the hepatic disease increases. Likewise, serum alkaline phosphatase activity remains within the normal ranges. The serum aspartate transaminase activity usually is high only in severely affected sheep. Similarly, sulfobromophthalein retention times often are altered in the most severely affected sheep. The half-life of sulfobromophthalein is prolonged, whereas the fractional clearance is less than normal.

Total serum protein concentrations gradually increase as the severity of the disease increases, but is usually substantially higher only in animals with severest lesions. In sheep, the increase is caused by a progressive increase in the γ-globulin fraction; the albumin concentration actually decreases in more severely affected sheep. α-Globulins are low in sheep at all stages of HFC, whereas β-globulins usually are only decreased in most severely affected sheep.

Mortality increases during each succeeding month following October, climaxes during January and February, and then decreases in the months thereafter. The months of January and February are the period during which the animals are subject to stresses of severe weather, terminal gestation, parturition, and lactation. Moreover, these 2 months are also the time that sheep are at the lowest plane of nutrition. In most pastures, morbidity varies from 86 to 100%. Mortality during a 12-month period varies from 10 to 60%. However, if a study of the mortality of sheep exposed during 1 year is extended to include a 3-year period, it may reach as high as 85%.

**Research Efforts**

Hepatic fatty cirrhosis develops in ruminants located predominantly in an isolated area in western and southern Texas during years with maximal rainfall. Interestingly, many other areas in western Texas have almost identical topologic, climatic, terrestrial, and vegetational features, yet HFC is not diagnosed in ruminants from these areas. It would seem that there may be a substantially larger region that would favor the establishment of HFC as an endemic disease. If so, HFC may pose a threat for domestic and wild ruminant production in these adjacent counties. Moreover, with the potential for interstate travel of livestock, the disease could easily be observed in ruminants outside of Texas. For these reasons, veterinarians in private practice as well as those at diagnostic laboratories and universities should be familiar with this disease. It has been suggested that if a rapid and accurate method of identification of animals with the early stages of the disease could be developed, this could greatly aid ranchers in making decisions on animal disposition or even alternative range usage.

The repeated, unsuccessful attempts to transmit the disease from animal to animal have virtually eliminated an infective agent as a plausible cause of HFC. Similarly, exhaustive efforts to identify an indigenous plant or plant toxin as the cause for HFC have been fruitless. To date, over 120 species of plants have been tested without the identification of any species capable of inducing disease or lesions similar to HFC. To be certain, there are several species of hepatotoxic plants native to this area. These include *Machaeranthera pinnatifida*, *Sartwellia flaveriae* (threadleaf sartwellia), *Senecio longilobus* (threadleaf groundsel), and *Senecio spartioides* var. riddelli. However, hepatic lesions associated with these plants are different than those seen with HFC. *Phyllanthus abnormis* has induced lesions similar to HFC, but it was never identified in the area where HFC is identified.

The finding of the fungus *Phomopsis leptostromiformis* growing on native grasses in the HFC endemic area is interesting, as this fungus is associated with sporadic diagnosis of lupinosis in domestic livestock in Australia, New Zealand, South Africa, and Europe. Lupinosis is a chronic, progressive hepatotoxicosis associated with a family of related toxins called phomopsins, which are potent, anti-
This form of lupinosis has not been recognized in the United States.

Animals affected with lupinosis have anorexia, weight loss, signs of depression, and icterus in the acute stages of the disease. Some animals may die in the acute phase after several days, but most develop a chronic disease, which progresses from fatty liver to hepatic cirrhosis over a period of months. These animals suffer from debilitation associated with severe weight loss and often die in hepatic coma. With the exception of the development of icterus in animals with lupinosis, these 2 diseases have many pathologic features in common.

In HFC, high aspartate transaminase activity and prolonged half-life and fractional clearance of sulfobromophthalein are indicative of impaired hepatic function accompanied by hepatocellular degeneration or necrosis. Sheep affected with HFC are typically hyperproteinemic, but this is attributed to the increase in the γ-globulin fraction. The amounts of albumin, α- and β-globulins, as well as fibrinogen in the plasma are inversely proportional to the degree of hepatic damage. Whereas γ-globulins have an extrahepatic source (lymphoid tissue), the decreases in albumin, α- and β-globulins, and fibrinogen are indicative of hepatic disease.

Icterus is not normally a feature of HFC, although the amounts of conjugated and unconjugated bilirubin do increase in the later stages of the disease. Similarly, serum alkaline phosphatase activity increases in the terminal phase of HFC, but not significantly. This is likely caused by interference with bile transport and excretion, resulting from the pronounced cirrhosis in the more terminal phases of the disease.

Although the cause of HFC has remained elusive, the clinical and epizootiologic features of the disease suggest a toxic cause—in the realm of a yet unidentified plant or possibly a mycotoxin. In support of the latter is the timing of the appearance of a fungus on range vegetation in winter and early spring. Ewes and lambs delivered during the winter develop clinical signs of HFC within 6 to 8 months. Moreover, the abundance of vegetation during the early months of the year would increase the dose of the toxin as well. This, followed by an overly dry summer with a reduced nutritional plane, could favor accelerated fat mobilization. The latter situation would potentiate the development of fatty change in an already diseased liver.

Current research efforts revolve around the fungus P. leptostromiformis, previously identified on native grasses. Interestingly, the toxin roridin A, originally reported to be isolated from this fungus, normally is a metabolite of a different fungus, Myrothecium roridum. This latter fungus has been responsible for natural poisonings, myrothecitoxocosis, which causes hemorrhagic abomasitis in sheep and calves in New Zealand.

References