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North American Hard Yellow Liver Disease: An Old Problem Readdressed

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North American Hard Yellow Liver Disease: An Old Problem Readdressed

Abstract

Hard yellow liver disease or fatty cirrhosis periodically affects cattle, sheep, goats, pronghorn antelope (*Antilocapra americana)* and whitetail deer (*Odocoileus virginianus texanus)* within several Texas counties in the United States. Clinically it presents as chronic liver disease with progressive hepatic necrosis and fibrosis, icterus and liver failure. The damaged livers are yellow and many have multiple firm, often gritty foci that are scattered throughout all lobes. Early investigations included feeding studies using potential toxic plants, climate and forage studies, infectious disease surveys and various mycotoxin studies and analyses. None have definitively reproduced the disease or identified the inciting cause. However, the problem continues and recent outbreaks have allowed the collection of additional frozen tissues, and numerous paraffin tissue blocks and slides for additional studies. The objectives for this work are to evaluate and compare the microscopic changes, special histochemical studies, microbial and fungal surveys and chemical assays for dehyro-pyrrolizidine alkaloid (DHPA) metabolites of these additional cases with historical reports. These bovine livers had a spectrum of lesions including lipid degeneration and necrosis, eosinophilic granulomatous hepatitis, focal follicular lymphoid proliferation and chronic fibrosing hepatitis with dystrophic mineralization. No pyrrolizidine alkaloid metabolites were detected in any of the livers and select special stains did not reveal any fungal, bacterial or parasitic etiologies. The lack of findings and mixed histologic presentation suggest that this syndrome is a collection of chronic diseases probably of various etiologies. Earlier animal surveillance work is needed in endemic areas to better understand the etiology and pathogenesis of this syndrome.

Keywords

Hard-Yellow-Liver-Disease, Lipogranulomatous-hepatitis, fatty-cirrhosis, lipid-hepatic-cirrhosis

Introduction:

Hard yellow liver disease (HYLD) or fatty cirrhosis is a poorly understood North American syndrome that was first described in 1931 (Dollahite *et al*. 1971). Initially it was reported to be a noninfectious disease of ruminants- cattle, sheep, goats, pronghorn antelope (*Antilocapra americana)* and whitetail deer (*Odocoileus virginianus texanus).* Outbreaks were generally limited to ruminants from, or that had been in several counties in western Texas. Though the incidence seems to have decreased from initial reports, it has been suggested that this is largely due to reduced reporting (Blankenship *et al.* 1976, Dollahite *et al.* 1971). Producers, veterinarians and abattoir inspectors in endemic areas recognize the disease; accept the related losses; and to a limited extent, have developed methods to minimize losses (personal communication M. Jones). Clinically HYLD is characterized by lipid hepatic cirrhosis with weight loss, icterus, emaciation, liver failure, hepatic encephalopathy and death. Cattle and sheep are most commonly affected and most cases are identified at slaughter when poor doing animals are culled; when clinically affected animals are biopsied; or when animals die and are examined post mortem. Reproductive failure is common and affected cows are often icteric with poor body condition that progresses to emaciation. The whole body observations at slaughter are similar as they include poor body condition, icterus with a firm hard liver that often has multifocal, coalescing, yellow lesions that depress the capsule and extend deep into the underlying parenchyma. Some have distinct margins resembling an infarct; however, no convincing vascular lesions have been identified (Dollahite *et al.* 1971; Helman *et al*. 1993).

HYLD is reported to occur sporadically in endemic areas at 4 to 7 year intervals. When it happens, incidence is often high and at times it can affect up to 90% of the ruminants in the range or pasture. Mortality can also be high with reports of losses of up to 75%. Deaths usually begin 3 to 4 months after exposure to associated pasture or range and most fatally exposed animals die within 12 months. Surviving animals remain hepatic cripples that may temporarily compensate for their decreased hepatic function only to die months or years later when animals relapse and develop hepatic failure.

Numerous etiologic agents have been proposed as causes of HYLD; however, none have been confirmed. Initial transmission studies concluded that it was not contagious, at least after animals developed clinical disease (Hardy *et al.* 1932). Later grazing experiments showed that although some premises were repeatedly associated with disease, this was not consistent. For example, after the initial outbreak, grazing studies were conducted on ‘disease premises’. Disappointingly, no hepatic disease was detected for that year and for several additional years until the summer of 1937 and 1941, which had small outbreaks of HYLD. Subsequent studies, several lasting more than 10 years, on the same premises did not produce disease (Hardy and Livingston 1964). Again in 1965

another outbreak occurred; however, subsequent grazing studies on affected properties similarly did not produce liver disease (Dollahite *et al*. 1971). Plant feeding trials for nearly 40 different plants collected from 'disease premises' were done using sheep. Of those, only five, *Senecio spartioides var. riddelli, S. longilobus, Sartwellia flaveriae, Phyllanthus abnormis,* and *Machaeranthera pinnatifida* produced liver disease, but none produced lesions similar to those of HYLD (Dollahite *et al.* 1971).

Subsequent HYLD studies had similar results. In 1979, Ueckert *et al.* continued grazing studies and in the winter produced hepatic necrosis in pregnant sheep kept on a range that historically had a high incidence of HYLD. However, other sheep ranged in the same location later that summer or in the subsequent year were not affected. They analyzed fecal material collected from the sheep in both years to determine if there were changes in their diet. They found forbs that were much more abundant the HYLD year with filaree (*Erodium texanum* and *E. cicutarium)* composing a relatively large portion of the affected sheep's diet. They also identified croton (*Croton* spp.), Nuttall milkvetch, tansymustard (*Descurainia pinnata),* silverleaf nightshade (*Solanum elaeagnifolium),* threadleaf groundsel (*Senecio longilobus),* locoweed (*Astragalus mollissimus),* bitterweed (*Hymenoxys odorata),* Trecul queen's delight (*Stillingia treculiana),* honey mesquite (*Prosopis glandulosa),* and tobosa grass (*Hilaria mutica)* with ergot (*Claviceps cinerea).* All of these are reported to be toxic and several are hepatotoxic [tansymustard (*Descurainia pinnata)* linked to heptatogenous photosensitization- Pfister *et al.* 1990; and threadleaf groundsel (*Senecio longilobus)* containing DHPAs- Johnson and Molyneux 1984.] But similar to previous feeding studies, when fed to sheep none produced hepatic disease similar to that seen in naturally occurring HYLD (Ueckert *et al*. 1979; Helman *et al.* 1993 and 1995).

Mycotoxins have also been considered as potential contributors to the development of HYLD. Though most analyses of feed from endemic ranges did not detect potential mycotoxins, in one survey a phomopsin, roridin A, was isolated from *Phomopsis* spp. (Samples *et al.* 1984). Roridin A is a trichothecene and though other hepatotoxic trichothecenes are hepatotoxic and cause ovine lupinosis (Gardiner 1965), roridin A toxicities in sheep did not produce liver disease (Thormahlen *et al.* 1994). Additionally as HYLD hepatic lesions are much different than both lupinosis and the described roridin-induced disease, it was concluded that the *Phomopsis* spp. were not likely to cause HYLD.

As some cases of HYLD have focal eosinophilic and granulomatous inflammation, it has been suggested that parasitism may be involved to some extent in its pathogenesis. A hepatic disorder characterized by multiple small yellow hepatic lesions termed 'bovine parasitic hepatitis' has been described in Japan. Nakamura used detailed histopathological examinations to identify fragments of degenerative parasite fragments; however, these were rarely identified in about 2%

of the affected Japanese cows (Nakamura 2005). Though no parasite fragments have ever been identified in HYLD, several potential parasites including *Capillaria*. and *Fasciola* spp. have been suggested, but never identified as potential causes.

Mycobacterium spp. hepatic infection has also been suggested as the cause of HYLD. *M. avium* subspecies *paratuberculosis* rarely produces focal granulomatous hepatitis in cattle (Smith *et al.* 2014). These organisms are acid fast and using special histochemistry small numbers have been identified *in situ* (Rodrigues *et al.* 2010; Driemeier *et al.* 1999). However, mycobacterial-induced lesions also differ from HYLD, as hepatic granulomas are rare and nearly always accompanied by more numerous lesions in other tissues. Additionally mycobacterial induced lesions are primarily inflammatory with little lipid degeneration and necrosis (Driemeier *et al.* 1999). In spite of extensive examination no convincing acid fast organisms (*Mycobacterium* spp.) were identified in any of the previous HYLD studies (Dollahite *et al.* 1971, Ueckert *et al.* 1979).

The objectives of this work are to examine recent cases of HYLD in cattle, describe the gross and microscopic lesions, investigate infectious or parasitic etiologies using special histochemical stains, chemically analyze liver for dehydropyrrolizidine alkaloid (DHPA) metabolites, and compare these lesions with those described previously.

Materials and Methods:

Since 1996 forty eight additional liver samples from cattle that were identified at slaughter having liver changes consistent with HYLD from various locations, producers, diagnostic laboratories and slaughter plants were collected. Most were slides with fewer numbers of paraffin blocks and formalin-fixed tissues; however, only 22 submissions included frozen liver. These were cattle between 3 and 11 years-old, mostly of mixed Angus breeding. Though none were sampled and included as a part of this review, other ruminants and wildlife have also been reported to develop similar disease.

Histopathology and Special Histology: Twelve of the newly acquired fixed tissues were embedded in paraffin, sectioned and stained with hematoxylin and eosin, Ziehl-Neelson carbol fuchsin acid fast, periodic acid-Schiff, Masson's trichrome, modified Grocott-Gomori methenamine silver nitrate, Brown and Brenn gram positive and congo red. All stains were done following standard techniques with freshly mixed reagents as published (Carson 1997).

DHPA Metabolite Chemical Analysis: Analysis were done on all 22 of the available frozen liver samples following minimal modifications of previously published methods *(*Brown *et al.* 2016*).* Briefly about 200 mg of freeze-dried liver was finely ground by including them in conical tubes with small copper coated steel

spheres that were shaken for 10 minutes in a Retech® MM301 shaker at 20 revolutions s^{-1}. Then 50 mg of the crushed, lyophilized liver was then placed into a plastic snap-cap conical tube after which ethanolic silver nitrate (1.0 mL) that was mixed for 30 min on an auto rotator. After mixing trifluoracetic acid (10 µL) was added and mixed overnight (~16 hrs) on an auto rotator. The samples were centrifuged at 16000 G for 10 min. and an aliquot of 100 µL of the supernatant was added to 850 µL absolute ethanol with 50 µL Ehrlich's reagent in an HPLC autosampler vial. LC-MS/MS analysis was accomplished using an Agilent 1260 Infinity HPLC System (Agilent Technologies, USA), a Synergi Hydro RP column and a Velos Pro LTQ mass spectrometer (Thermo Scientific, USA) following previously described elution and detection conditions (Brown *et al.* 2016). Under these conditions the "pyrrole"-Ehrlich's reagent compound eluted with a retention time of 4.4 min and the resulting MS/MS spectrum contained major fragment ions at *m/z* 252 and 296. Tissues from previous studies of DHPA toxicity in livestock were used as positive controls that consistently produced the "pyrrole" peak with a reconstructed ion chromatogram displaying *m/z* 296 that could be quantitated.

Results:

Most of the cattle included in this review were culled as non-pregnant cows in poor condition. All were icteric and at slaughter their livers were hard with multifocal, coalescing, yellow firm lesions that depressed the capsule and extended deep into the underlying parenchyma (Figure 1). Though some lesions involve the entire liver with multiple pale firm foci (Figure 2), none were diffusely swollen and yellow as is often reported and described (Dollahite *et al.* 1971, Ueckert 1979).

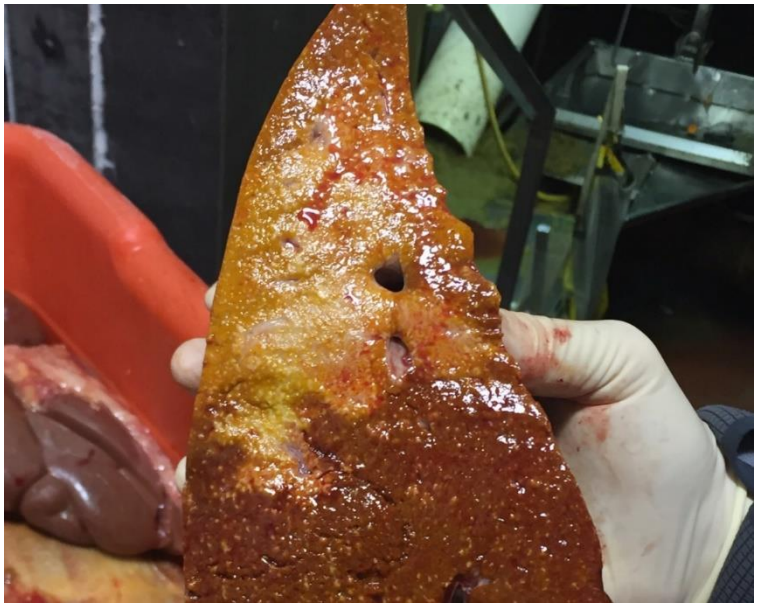

Figure 1. Liver from a cow identified as having hard yellow liver disease at slaughter. Notice the yellow, hard, firm lesion that extend from the capsule deep into the hepatic lobe. Much smaller 1 to 2 mm yellow lesions are also scattered through the more normal areas of the liver.

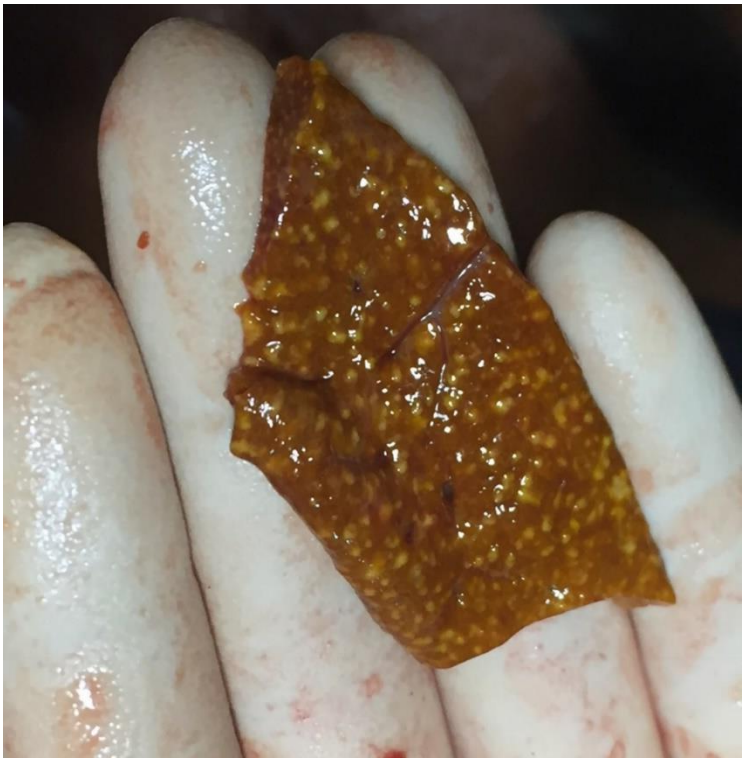

Figure 2. Photograph of a cut section of liver from a cow that was identified as having hard yellow liver disease at slaughter. Notice the small 1 to 2 mm firm yellow foci scattered throughout the liver.

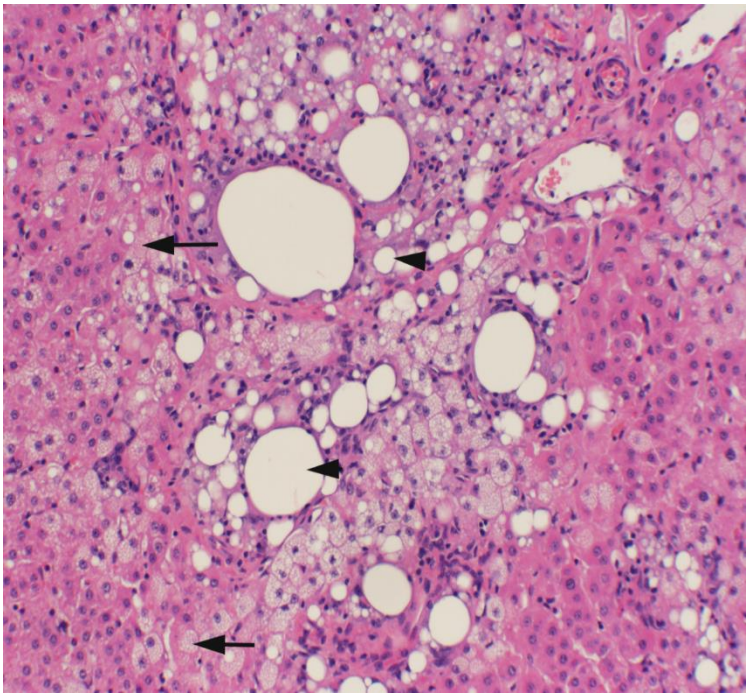

Figure 3. Photomicrograph of a section of liver from a cow identified at slaughter as having hard yellow liver disease. Notice the focally extensive hepatocellular swelling and degeneration with cytoplasmic distension with fine, granular cytoplasmic vacuolation (arrows) that leads to the formation of large lipid vacuoles (arrowheads). Notice also the lymphocytic infiltrates, proliferative fibroblasts (H&E).

The microscopic findings in these cattle were variable and often seemed to be stage dependent and progressive. Early hepatic lesions were degenerative with portal hepatocellular swelling and cytoplasmic accumulation of fine lipid vacuoles (Figure 3).

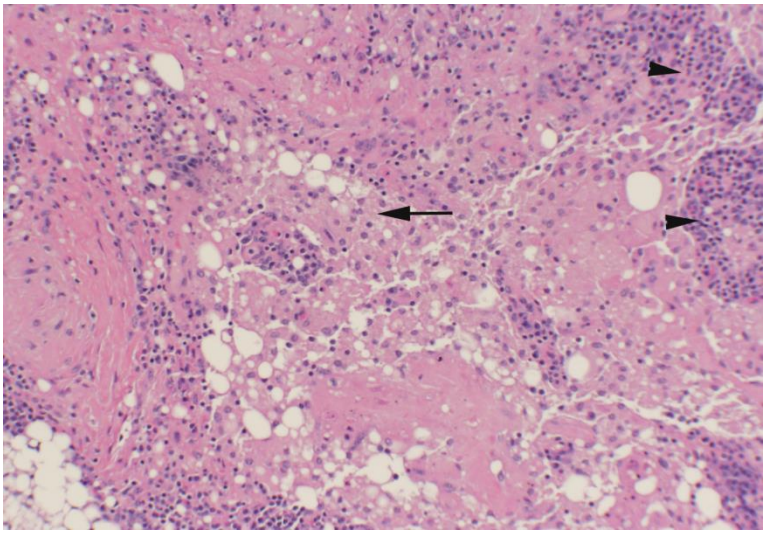

Figure 4. Photomicrograph of a section of liver from a cow identified at slaughter as having hard yellow liver disease. Notice the focally extensive necrosis (arrow) with subsequent chronic inflammation (arrowheads). There are formations of numerous lipid vacuoles and the margins often contain proliferative fibrous connective tissue (H&E).

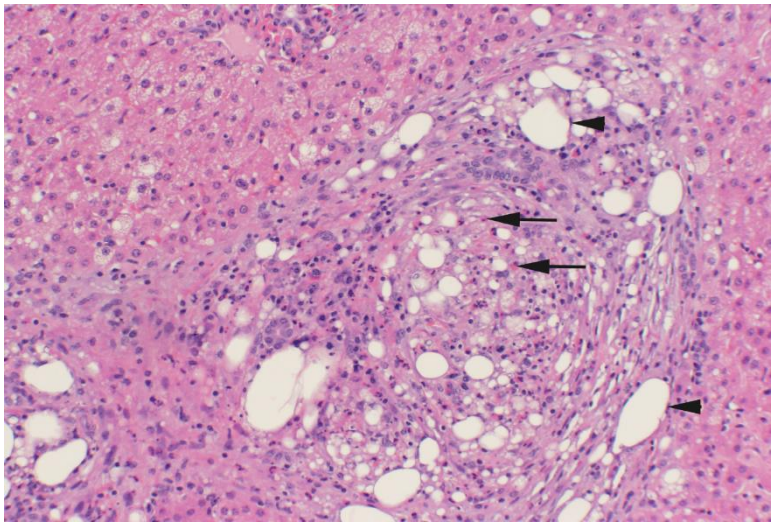

Figure 5. Photomicrograph of a section of liver from a cow identified at slaughter as having hard yellow liver disease. Notice the focal inflammation that is characterized by central necrosis surrounded by macrophages with small clusters of lymphocytes and rare eosinophils (arrows). Numerous lipid vacuoles are present (arrowheads) and small numbers of entrapped bile ducts are present in the surrounding proliferative fibrous connective tissue (H&E).

These lipid vacuoles appear to fuse and form large lipid vacuoles as more severely affected hepatocytes become necrotic with pyknotic nuclei and cellular disruption. The supporting connective tissue is expanded with fibroblast proliferation and early fibrosis that often has infiltrates of lymphocytes with small numbers of neutrophils. More extensive lesions include extensive hepatocellular necrosis with loss and collapse of hepatic cords, pools of necrotic hepatocytes and cellular debris, clusters of lymphocytes and macrophages and bands of fibrous connective tissue (Figure 4). In some animals the inflammation becomes variable with clusters of eosinophilic and even granulomatous inflammation (Figure 5). Livers from other cows have zones of lymphocytic inflammation with lymphocytic and plasmacytic clusters that are often expanded with homogenous eosinophilic material that is consistent with amyloid (Figure 6). Nearly all lesions have extensive proliferation of fibrous connective tissue that often entraps surviving degenerative hepatocytes resulting in piece meal necrosis. Chronic lesions have extensive and often bridging fibrosis with chronic inflammation and multifocal dystrophic mineralization (Figure 7). These lesions also have extensive biliary hyperplasia and increased numbers of biliary profiles as the lobules collapse. Of these progressive and different inflammatory, fibrotic, and regenerative changes, lipid vacuoles are always present in their number and size seem to reflect lesion severity.

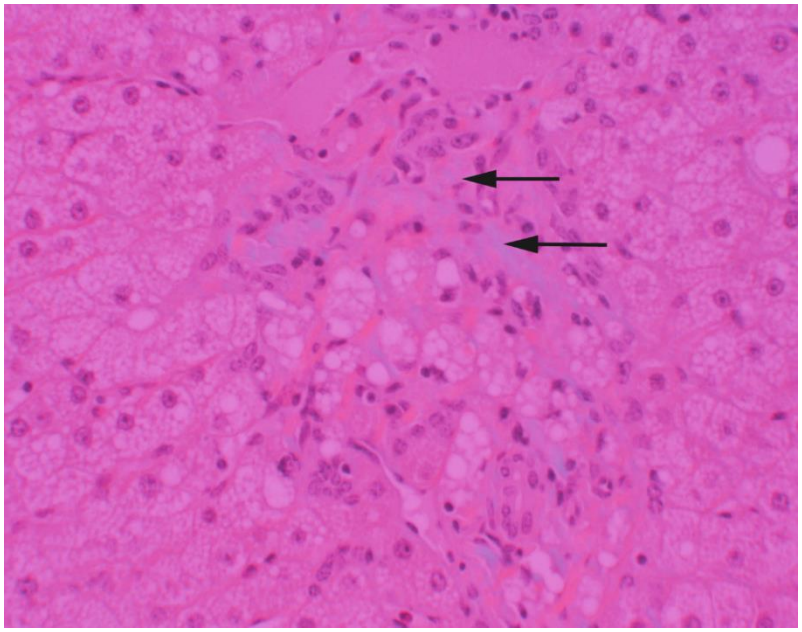

Figure 6. Photomicrograph of a bovine hard yellow liver disease liver stained with Congo red and illuminated with polarized light. Though using this light the resolution is poor, it does illustrate the small green birefringent zones (arrows). This material is seen as homogenous eosinophilic material in H&E stained sections and it is closely associated with lymphocytic and plasmacytic inflammation. Though such birefringence is not specific for amyloid, the histologic nature, birefringence with polarized light and association with plasma cells and lymphocytic inflammation is highly suggestive of amyloid (Yakupova *et al*. 2019).

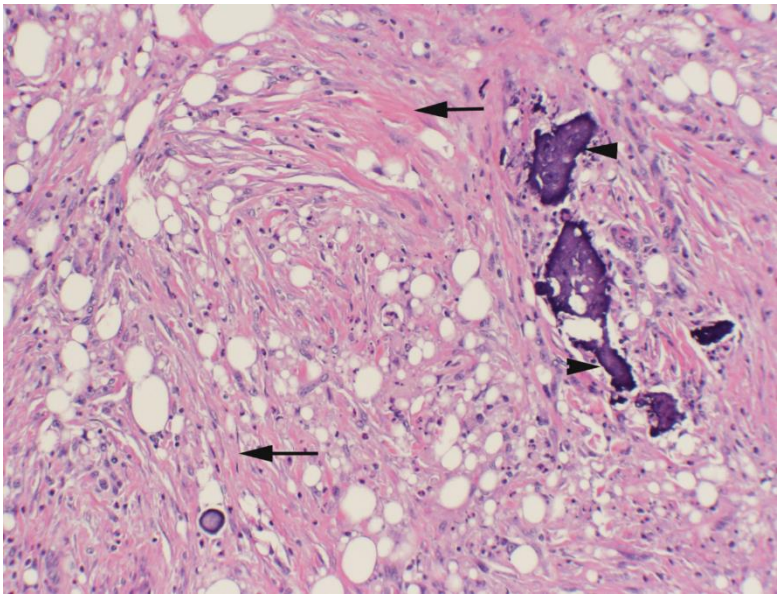

Figure 7. Photomicrograph of liver from a cow identified at slaughter as having hard yellow liver disease. Notice the focally extensive fibrosis (arrows) with foci of dystrophic mineralization (arrowheads). The mineralized necrotic debris is surrounded by chronic inflammation with macrophages and lymphocytes. No recognizable hepatocytes are present in this image (H&E).

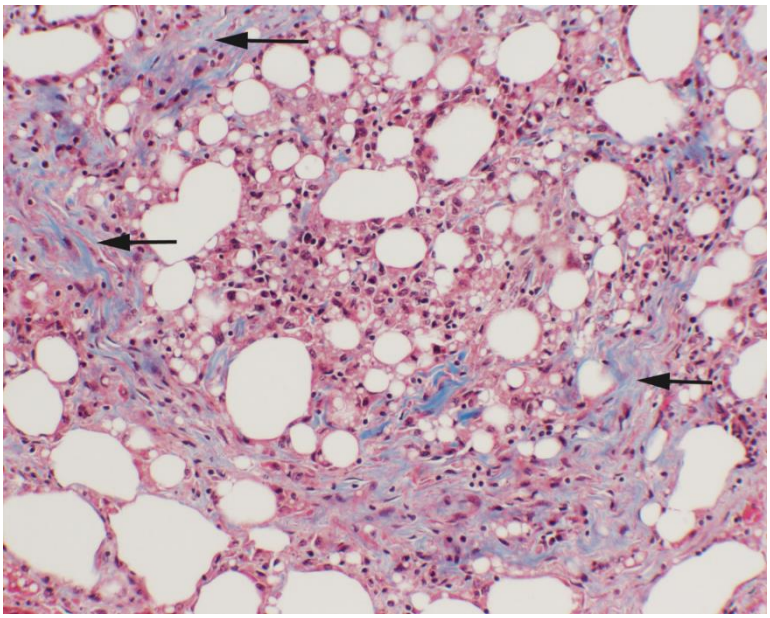

Figure 8. Photomicrograph of liver from a cow identified at slaughter as having hard yellow liver disease stained with Masson's trichrome. Notice the central zone of necrosis surrounded by proliferative fibroblasts and small amounts of blue staining collagen (arrows). Numerous lipid vacuoles are present throughout the section.

Special histochemistries of these livers did not identify any microorganisms, parasites or foreign material. The Masson's trichrome histologic stain highlighted the proliferative fibrous connective tissue that surrounded necrotic zones (Figure 8). The Congo red stain, which has been used for identifying amyloid-like material, demonstrated rare patchy green birefringence of within the eosinophilic material near and within lymphocytic inflammation (Figure 6). The

acid fast, periodic acid-Schiff, methenamine silver, and Brown and Brenn stains are used to help identify microorganisms, fungi, parasites, and foreign material in sections. All of these sections were closely examined and no convincing etiologic agents were identified. None of the chemical extractions of the HYLD livers contained DHPA metabolites.

Discussion:

North American hard yellow liver disease (HYLD) continues to be a localized problem in certain counties of Texas. These relatively new cases are similar to those described historically and demonstrate the variable nature of the microscopic lesions (Figures 3-7) (Dollahite *et al.* 1971, Ohlenbusch 1990, Uechert *et al.* 1979). The mixed nature of the inflammatory lesions was remarkable ranging from lymphocytic inflammation and proliferation to granulomatous and focally eosinophilic inflammation. There was also variable lesions distribution ranging from infarct-like circumscribed lesions to diffuse hepatocellular degeneration. The necrosis and subsequent fibrosis was also variable ranging from focal to extensive with dystrophic mineralization. All of this variability suggests that this syndrome is chronic liver disease caused by a collection of etiologies. Probable etiologies are similar to those suggested previously including toxic plants (Ueckert 1979), parasites (Nakamura 2005), mycotoxins (Samples *et al.* 1984, Thormahlen *et al.* 1994), metabolic or lipid mobilization abnormalities (Blankenship *et al.* 1976, Wieckowska *et al.* 2007), climate or vegetative changes (Ohlenbusch 1990), *Mycobacterium* spp. or other bacterial infections (Alcantara-Payawal *et al.* 1997, Hibiya *et al.* 2010, Smith *et al.* 2014), and other idiopathic processes (Brunt 2001, Rubinstein and Brenner 1982). As in previous reports none of the current special histochemistries identified potential bacterial or fungal organisms. Certainly more work including early monitoring such as serum biochemical surveys and liver biopsies are needed to better define and characterize the pathogenesis of this disease.

As mentioned various toxic plants have been associated with HYLD (Ueckert *et al.* 1979). Of these DHPA containing plants seems the most likely prospect. However, none of these cows or any of those described in previous reports had microscopic lesions similar to those described in DHPA intoxication (Stegelmeier *et al.* 1999). In this study no DHPA metabolites were detected in any of the livers analyzed. This suggests that it is unlikely that DHPA containing plants are involved in the pathogenesis of HYLD.

A novel HYDL observation unique to these recent cases is that some animals (4 of the 12 that were examined microscopically using the battery of special stains) had zones granulomatous and follicular lymphocytic proliferation and plasma cells with homogeneous eosinophilic material that is most likely amyloid (Figure 6). This has not been previously described and suggests that might be an

immune or hypersensitivity component to the disease in these animals. Though HYLD appears to be confined to the liver, similar systemic granulomatous lesions with lymphoid proliferation are commonly seen in hairy vetch (*Vicia villosa)*-associated granulomatous inflammatory disease (Panciera *et al.* 1992). Additional work is needed to determine if a hypersensitivity reaction with T-lymphocyte induced cellular response and inflammation similar to vetch are involved in the progression of some HYLD lesions. Though the cause of vetch induced disease is also unknown, common mechanistic methods might be helpful in identifying the cause and pathogenesis of both processes.

Other potentially toxic hepatopathies of unknown cause have been identified in other countries. For example, Australian acute bovine liver disease (Aslani *et al.* 2006) is a syndrome characterized by fatal hepatopathy and photosensitization. Less localized than HYLD, it has been reported in several different geographic regions of Australia. Clinically some poisoned animals have decreased milk production, photosensitization, and unexplained death. Other may develop pyrexia, loss of appetite, oral and anal mucoid exudates and jaundice. Post mortem examinations demonstrate hemorrhages on many serosal surfaces and along vessels. The liver is enlarged, soft and friable. Histologically there is periportal hepatocellular necrosis with biliary proliferation (Aslani *et al.* 2006). Poisoning has been associated with rough dog's tail grass *(Cynosurus echinatus*) and mycotoxins of *Drechslera biseptata.* Similar to HYLD the cause of this potential intoxication has not been definitively proven and certainly may have similar etiologies to HYLD. Further work is needed to determine if these and others have similar etiologies and to identify the toxin and pathogenesis of these syndromes.

HYLD cases as reported by previous investigators and all of these cases are characterized by extensive lipid cirrhosis and chronic, end-stage liver failure. Cirrhosis is a non-specific hepatic response and can be the result of many different toxins, parasites, microbes, and even nutritional and immunologic diseases (Cattley and Cullen 2013). The resulting diagnostic challenge is that the etiology specific pathology and even potential agents are often obscured by cirrhotic fibrosis and regeneration. Certainly a more productive approach to better characterize this disease would be early detailed animal health surveillance and preclinical evaluations with mineral analyses, serum biochemistries, appropriate microbiology, parasite isolations, liver biopsies, survey necropsies with histologic examinations of complete tissue collections.

Conclusions:

These relatively new cases are similar to previously reported cases of HYLD. As in previous studies, no etiologic were detected in these samples. Though dehydropyrrolizidine alkaloids containing plants have been identified in endemic

areas, dehydropyrrolizidine alkaloid metabolites were not detected, suggesting in these cases these plants probably do not contribute to HYLD. These histologic studies as did the reported studies demonstrate that hard yellow liver disease is variable with a spectrum of pathology. This suggests that this syndrome is probably a collection of different diseases that will continue to require additional research and investigation to identify, sort and characterize.

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