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Grading and Staging of Hepatic Lesions in Dairy Cows: Insights on Toxicity

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One of the biggest dairy complexes is located at Tizayuca Hidalgo Mexico where an increase of hepatic fibrosis has been reported. However, little is known about microscopic lesions related to it. Since available standardized scoring systems for grading hepatic necroinflammatory activity and staging of fibrosis provide a framework to clarify aspects of pathogenesis, formalin-fixed, paraffin-embedded, H&E-stained liver samples from 50 cows with macroscopic lesions were microscopically evaluated for grading and staging of hepatic lesions of dairy cattle from Tizayuca, Hidalgo. Grading of necroinflammatory activity was scored from 0-18 based on severity and extent of interface necrosis, portal inflammation, focal necrosis and/or inflammation, and confluent necrosis. Stage of fibrosis was scored from 0-6 based on the extent and distribution of fibrosis present. Both confluent and interface necrosis were common as well as portal inflammation with marked bile duct hyperplasia. In general, grading and staging range from mild to moderate and initial to progressive, respectively. Few cases exhibited terminal fibrosis and/or cirrhosis. Both grading and staging range from mild to moderate. The findings are suggestive of toxic damage either by products of biotransformation (zone 3) or by direct acting toxins (zone 1), most likely, aflatoxins. On the other hand, lipidosis due to intensive milk production may have promoted a higher susceptibility to toxic damage since it was found in 27% of the cases with severe lesions. The system for standardized evaluation of bovine chronic liver disease was useful, but assessment of the relationship of this scheme to toxicity requires further investigation.

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Lymphosarcoma With Respiratory and Oral Cavity Epitheliotropism in a Boa Constrictor

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A 20 year old captive male Boa constrictor (*Boa constrictor constrictor*) died after a 7 month history of anorexia and weight loss. There were no significant clinical pathologic or radiologic findings prior to death, and no known health problems prior to the onset of anorexia and weight loss. Necropsy revealed a thin snake with atrophied fat bodies. The lungs were diffusely light tan and severely consolidated. Petechiae were present on the mucosa of the oral cavity, laryngeal mound, and intrapulmonary trachea of the right lung, and sporadically in the mucosa of the stomach, duodenum, and terminal colon. The spleen was light tan, enlarged, and had a nodular texture. Histologically, sheets of neoplastic lymphocytes completely effaced the architecture of the spleen. Coalescing infiltrates of neoplastic lymphocytes were also present in the faveolar interstitium of the lung and submucosa of the trachea, larynx, and oral cavity, and less frequently in the submucosa of the esophagus and gastrointestinal tract. In the pulmonary parenchyma, trachea, larynx, and oral cavity, the neoplastic lymphocytes infiltrated the mucosal epithelium, and formed discrete aggregates resembling Pautrier's microabscesses. Mucosal necrosis, ulceration, and hemorrhage in these tissues correlated with petechiae noted grossly. No other tissues contained neoplastic lymphocytes. Attempts to label the cells immunohistochemically using monoclonal antibodies against human CD3, CD4, CD45RA, and CD20 were not successful. The specific site of origin of the neoplasm could not be determined. Lymphosarcoma is one of the more common neoplasms in snakes, and is typically multicentric. Oral cavity involvement is common. However, to the authors' knowledge, epitheliotropism has not been reported in cases of lymphosarcoma in snakes or other reptiles.

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Diacetyl Increases Sensory Innervation and Substance P Production in Rat Trachea

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Vapors of butter flavor often contain diacetyl, an alpha-diketone that imparts the aroma and flavor of butter. Diacetyl causes epithelial necrosis and inflammation in rat and mouse airways. Diacetyl-exposed workers can develop fixed airway obstruction, but some exposed workers have symptoms of other conditions including self-reported wheezing. Pharmacokinetic modeling indicates that, at given vapor concentrations, the rat trachea receives comparable doses to human intrapulmonary airways following diacetyl inhalation. Substance P (SP) in sensory neurons plays a critical role in airway hyperresponsiveness and inflammation. Therefore, we investigated the hypothesis that diacetyl inhalation alters sensory innervation and SP production in airway epithelium. Neurons in jugular and nodose ganglia projecting to the airways were retrogradely labeled by tracheal instillation of rhodamine microspheres. Rats (6/group) were exposed to 0, 25, 249, or 346 ppm diacetyl for 6 h. One day post-exposure, ganglia and upper trachea were processed for SP immunofluorescence. SP immunoreactive sensory nerve fibers and cell bodies were measured by morphometry. Diacetyl inhalation caused a dose-dependent increase in the number of SP immunoreactive airway neurons in jugular ganglia from 3.26 ± 3.0 (control) to 14.70 ± 5.9, 22.70 ± 8.4, and 25.5 ± 6.6 at 25, 249 and 346 ppm, respectively. In trachea, after inhaling 346 ppm diacetyl, sensory nerve fiber density was unchanged in the fields with intact epithelium. However, the innervation was significantly increased in the intact epithelium adjacent to denuded foci (5.7 fold) and in foci with detaching epithelium (3.3 fold). These findings suggest that acute diacetyl inhalation causes dose-dependent SP production in airway neurons of jugular ganglia and increased epithelial innervation in tracheal foci with specific types of epithelial injury.

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CD81 Antibody-Induced Syncytia Formation in a Human Hepatocyte Chimeric Mouse Model

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Antibodies targeting cell surface proteins have been proposed as agents to block viral receptors to treat persistent viral infections. CD81 is critical for human hepatitis C virus (HCV) entry into human hepatocytes. Testing the efficacy of HCV antiviral therapies in vivo is challenging because animal models, outside of the chimpanzee and genetically modified animals, do not support HCV replication. In a study designed to test the efficacy of anti-CD81 for the treatment of HCV using the uPA/SCID mouse model with transplanted human hepatocytes, we detected elevations in serum alanine transaminase (ALT) activity which corresponded with histologic findings of syncytia formation. Syncytia were observed only within human origin hepatocytes and were observed with multiple anti-human CD81 antibodies. Antibody treatment reduced the proportion of human hepatocyte engraftment within mouse livers. The mechanism of the syncytia formation is undetermined, but may be an artifact of the chimeric mouse model. Further investigation is warranted to explore the potential for undesirable effects of antibodies which target CD81 as a therapy for HCV infection.