



Latin Comparative Pathology Group

The Latin Subdivision of the CL Davis Foundation

Diagnostic Exercise

Case #: 48 Month: September Year: 2014

Answer Sheet

Contributor: Ricardo Ochoa, DVM, PhD, DACVP

Clinical History: Photomicrographs from a Göttingen minipig that died during a 28-day toxicity assessment study for an undisclosed small molecule.

Diagnosis: This is a case of disseminated vasculitis in the minipig. The diagnosis of thrombocytopenia could not be made because there were no terminal samples obtained. However these findings are characteristics of the spontaneous occurrence of thrombocytopenic purpura in minipigs.

Typical Gross findings: The classical presentation at necropsy is a described in the necropsy findings in this animal. There are multiple petechial and sometimes ecchymotic hemorrhages in many of the organs. Thrombocytopenic purpura in minipigs classically affects the skin, heart, urinary bladder, intestine, kidney and lung.

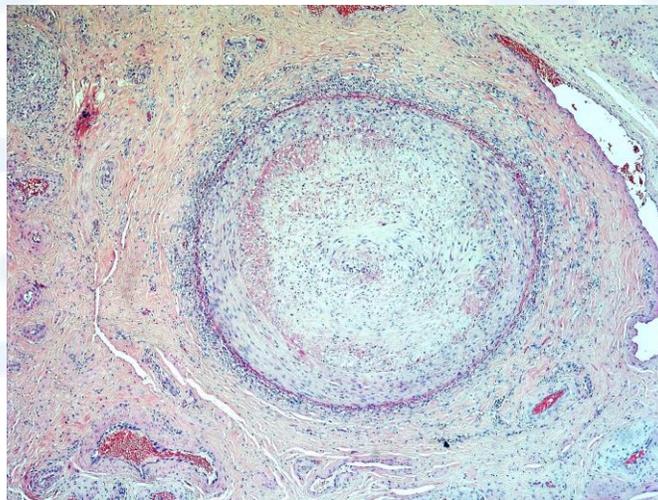


Figure 1. Cervix wall, Modified Trichrome stain, 5X. For more histological images, please see the first part of the submission.

Typical microscopic findings:

- Vasculitis in the arterioles and small- to medium- sized muscular arteries, most observed in the renal pelvis and heart.
- Presence of tunica media necrosis, as well as degeneration and intimal proliferation, depending on the duration of the condition.
- Concentric laminar thickening of vessel walls in an “onion-skin” pattern.
- Thrombocytopenia and anemia are also often found.

Discussion:

This case is presented because it is important to keep in mind that these conditions can occur spontaneously in minipigs (i.e. background finding). The minipig is increasingly becoming a species of choice for many toxicology studies. However, many pathologists are less familiar with spontaneous diseases of minipigs. This condition has been diagnosed in regular pigs and has been suggested as an animal model for VonWillenbrand’s disease. The presence of increased globulin in this animal two weeks before death may be an indication of some autoimmune mechanism being at play. The lack of understanding of the pathogenesis of a condition often results of the study pathologists’ inability to ultimately determine the relationship to compound treatment.

In this case, the conclusion that this vasculitis was not compound related. Other than the references in the literature of it being a spontaneous change, in this case the conclusion was also aided by the fact that this animal was in the mid-dose group, without similar occurrences in the high dose (i.e. lacking dose-relationship).

Vasculitis is of particular importance since any vasculitis in animals induced by the compound constitutes an alarming finding. Vasculitis in humans can often be silently lethal, and there are no good biomarkers to monitor its appearance in patients. Although vasculitis produces clinicopathological changes such as increases in reactive C protein and other stress biomarkers, these are not specific to vasculitis.

This case is also useful to illustrate how important it is to collect pre-mortem samples for clinical pathology from animals dying in toxicology studies prior to the scheduled euthanasia. Often there is lack of understanding of the

importance of this step, as some people argue that there are no control values obtained at the same time and therefore the data would be “uninterpretable”.

References and Recommended literature

1. Zubal, D and Skydsgaard, M 2012. Spontaneous/Background Pathology of Gottingen Minipig in: McANulty, PA, Dayan, AD, Ganderup, N-C, and Hastings, KL: The Minipig in Biomedical Research CRC press, Taylor and Francis Editors pp 306-307
2. Carrasco, L. Madsen LW. Alguero, FJ. Nunez, A, Sanchez-Cordon, P. and Bollen,P. 2003 Immune Complex-associated Thrombocytopenic Purpura Syndrome in Sexually Mature Gottingen Minipigs J Comp Pathol 128: 25-32
3. Maratea, K.A. Snyder, P.W. Stevenson G.W. 2006 Vascular Lesions in Nine Gottingen Minipigs With Thrombocytopenic Purpura Syndrome Vet Pathol (43) 447-454
4. Fuster, Valentin and Bowie, Walter E.J. 1979, Von Willebrand's Disease in Pigs and Atherosclerosis. Ricerca in clinical e laboratorio, (9) 319-320

Please send your comments/questions to the whole LCPG list by hitting “reply to all”.

A final document containing this material with answers and a brief discussion will be posted on the C. L. Davis website by the end of the current month (http://www.cldavis.org/lcpg_english.html).