CMHD Pathology Report

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Europhenome

ReportID: Report Date: October 08, 2013
Pathologist: Dr. H. Adissu

CMHD LabID: N13-697

Relevant History:
Phenotype:

increased susceptibility to bacterial infection
preweaning lethality
embryonic lethality
aphakia
iris hypoplasia
small lens

AnimalID: M00615039 (Male)

Histopathology Findings:

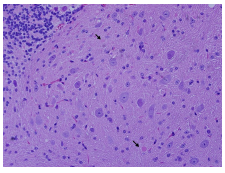
brain (MA:0000168)

Histopath Description:
Within the deep cerebellar nuclei are numerous eosinophilic, amorphous granular spheroid/globular bodies that are 10-25 um in diameters. There is no cellular reaction in these areas. The lateral ventricles are mildly dilated.

Morphological Diagnosis:
Distribution: multifocal; **MPATH Process Term:** degenerative change MPATH:14

Definitive Diagnosis:
Eosinophilic spheroids in dorsal medullar nuclei

Histopathology Comments:
See line summary for comments on this lesion. Mild dilation of the lateral ventricles is a background condition in mice of C57BL/6N background (Brayton et al., 2004).



Brain, deep cerebellar nuclei, eosininophilic spheroids, 40x, HE

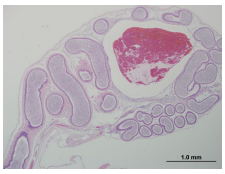
epididymis (MA:0000397)

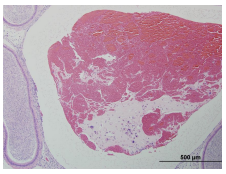
Histopath Description:
Within the interstitium in the tail of the epididymis is a large (2 mm diameter) blood-filled cyst that is lined by occasional endothelial cells. The cyst also contains cellular and nuclear debri. There are moderate numbers of inflammatory cells (mainly lymphocytes and few granulocytes) within the surrounding interstitium.

Morphological Diagnosis:
Distribution: focally extensive; **MPATH Diagnosis:** cyst MPATH:62; **MPATH Process Term:** degenerative change MPATH:14

Definitive Diagnosis:
Epididymal hemocyst

Histopathology Comments:
This is an unusual lesion is likely caused by cystic dilation of a vein. The lesion is considered incidental. Scrotal hemocysts are reported in humans.


Epididymis, hematocyst, 4x, HE

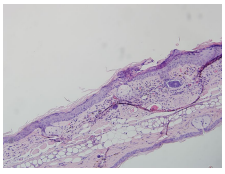

Epididymis, hematocyst, 10x, HE

ear (MA:0000236)

Histopath Description:
Multifocally there are serocellular crusts (scabs) on the ear skin. There are low numbers of mononuclear and rare polymprphonuclear inflammatory cells cells within the dermis. The epidermis is multifocally hyperplastic.

Morphological Diagnosis:
Distribution: multifocal; **Severity:** mild; **MPATH Diagnosis:** inflammation MPATH:212; **MPATH Process Term:** inflammation MPATH:212

Definitive Diagnosis:
Dermatitis with epidermal hyperplasia


Skin, dermatitis, 20x, HE

liver (MA:0000358)

Histopath Description:
diffuse lipidosis

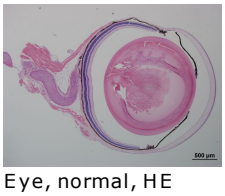
Morphological Diagnosis:
Distribution: diffuse; **Severity:** extreme; **MPATH Diagnosis:** steatosis MPATH:622; **MPATH Process Term:** lipid deposition MPATH:42

Definitive Diagnosis:
hepatic steatosis

eye (MA:0000261)

Histopath Description:
Normal

Definitive Diagnosis:
Normal


Eye, normal, HE

Organ/Tissue Analyzed:
Histopathology examination included the following organs and tissues: brain, trigeminal ganglion, eyes, salivary glands, trachea, lungs, heart, thymus, thyroid gland, parathyroid gland, exocrine and endocrine pancreas, oesophagus, stomach, small intestine, large intestine, liver, gall bladder, spleen, kidneys, adrenal gland, lymph nodes, spinal cord, bone marrow, sternum, femur and tibia with associated skeletal muscles, brown fat, pinna, skin, testis, epididymis, seminal vesicle, and prostate.

AnimalID: M00615041 (Male)

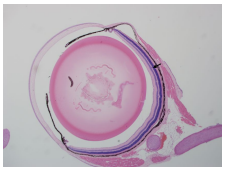
Histopathology Findings:

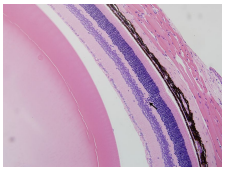
retina (MA:0000276)

Histopath Description:
Focal aggregates of external nuclear cells within the outer plexiform layer.

Morphological Diagnosis:
Distribution: multifocal; **Severity:** mild;

Definitive Diagnosis:
Retinal folding (dysplasia)


Eye, retina, focal dysplasia, 4x, HE


Eye, retina, focal dysplasia, 20x, HE

thymus (MA:0000142)

Histopath Description:
There is a 50 um diamater epithelial cyst within the medulla.

Morphological Diagnosis:
Distribution: focal; **MPATH Diagnosis:** cyst MPATH:62; **MPATH Process Term:** developmental and structural abnormality MPATH:55

Definitive Diagnosis:
Epithelial cyst

Histopathology Comments:
This is a developmental abnormality commonly seen in mice.

liver (MA:0000358)

Histopath Description:
diffuse lipidosis

Morphological Diagnosis:
Distribution: diffuse; **Severity:** extreme; **MPATH Diagnosis:** steatosis MPATH:622; **MPATH Process Term:** lipid deposition MPATH:42

Definitive Diagnosis:
hepatic steatosis

Organ/Tissue Analyzed:
Histopathology examination included the following organs and tissues: brain, trigeminal ganglion, eyes, salivary glands, trachea, lungs, heart, thymus, thyroid gland, parathyroid gland, exocrine and endocrine pancreas, oesophagus, stomach, small intestine, large intestine, liver, gall bladder, spleen, kidneys, adrenal gland, lymph nodes, spinal cord, bone marrow, sternum, femur and tibia with associated skeletal muscles, brown fat, pinna, skin, testis, epididymis, seminal vesicle, and prostate.

AnimalID: M00384553 (Female)

Histopathology Findings:

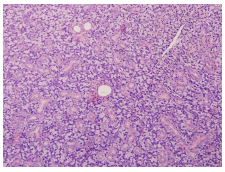
salivary gland (MA:0000346)

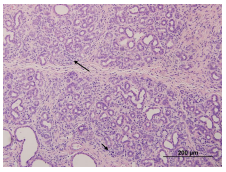
Histopath Description:
Unilaterally, the interstitium of the mandibular gland is expanded by fibrosis and mild to moderate numbers of lymphocytic infiltrates that also separate acini and ducts. The salivary acini are devoid of secretory granules and their lumina are dilated. There are occasional large glandular cells with large basophilic nuclei (up to 2x normal) (cytomegaly and karyomegaly).

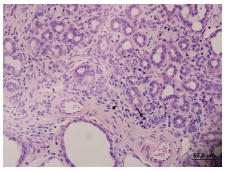
Morphological Diagnosis:
Duration: chronic; **Distribution:** unilateral; **Severity:** severe; **MPATH Process Term:** inflammation MPATH:212

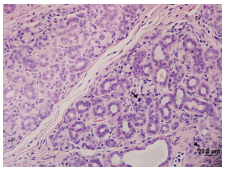
Definitive Diagnosis:
lymphocytic sialoadenitis with karyomegaly and intranuclear inclusions

Histopathology Comments:
Karyomegalyly with intranuclear inclusions in acinar epithelial cells with lymphoplasmacytic infiltration of interstitium is highly suggestive of infection by Mouse Cytomegalovirus (MCMV).


Mandibular salivary gland, contralateral, normal, 20x, HE


Mandibular salivary gland,lymphocytic sialoadenitis with karyomegaly, 20x, HE


Mandibular salivary gland, inflammation, note karyomegaly, 40x, HE


lMandibular salivary gland, karyomegaly and intranuclear inclusions, 40x, HE

stomach (MA:0000353)

Histopath Description:
mild neutrophilic gastritis; there is also mild epithelial proteinosis

Morphological Diagnosis:
Distribution: multifocal; **Severity:** mild; **MPATH Process Term:** inflammation MPATH:212

Definitive Diagnosis:
Mild neutrophilic gastritis with epithelial proteinosis

liver (MA:0000358)

Histopath Description:
diffuse lipidosis

Morphological Diagnosis:
Distribution: diffuse; **Severity:** extreme; **MPATH Diagnosis:** steatosis MPATH:622; **MPATH Process Term:** lipid deposition MPATH:42

Definitive Diagnosis:
hepatic steatosis

spleen (MA:0000141)

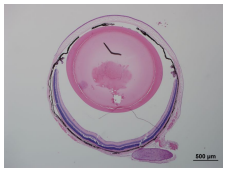
Histopath Description:
moderate erythropoiesis

Morphological Diagnosis:
Distribution: multifocal to coalescing; **Severity:** moderate; **MPATH Diagnosis:** extramedullary hemopoiesis MPATH:595; **MPATH Process Term:** hyperplasia MPATH:134

Definitive Diagnosis:
Moderate erythropoiesis

eye (MA:0000261)

Histopath Description:
Normal


Eye, normal, 4x, He

Organ/Tissue Analyzed:
Histopathology examination included the following organs and tissues: brain, trigeminal ganglion, eyes, salivary glands, trachea, lungs, heart, thymus, thyroid gland, parathyroid gland, exocrine and endocrine pancreas, oesophagus, stomach, small intestine, large intestine, liver, gall bladder, spleen, kidneys, adrenal gland, lymph nodes, spinal cord, bone marrow, sternum, femur and tibia with associated skeletal muscles, brown fat, pinna, skin, uterus, oviduct, and ovary, and mammary gland.

AnimalID: M00384554 (Female)

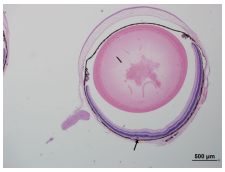
Histopathology Findings:

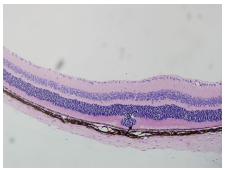
retina (MA:0000276)

Histopath Description:
There is a focal polypous outgrowth of the outer nuclear layer into the rods and cons layer. Other ocular structures are within normal limits

Morphological Diagnosis:
Distribution: focal; **Severity:** mild; **MPATH Process Term:** developmental and structural abnormality MPATH:55

Definitive Diagnosis:
Retinal folding (dysplasia)


Eye, retina, focal dysplasia, 4x, HE


Eye, retina, focal dysplasia, 20x, HE

brain (MA:0000168)

Histopath Description:
There is mild dilation of the lateral ventricles

Morphological Diagnosis:
Distribution: bilateral; **Severity:** mild; **MPATH Process Term:** degenerative change MPATH:14

Definitive Diagnosis:
Dilation of the brain ventricles

Histopathology Comments:
Mild dilation of the lateral ventricles is a background condition in mice of C57BL/6N background (Brayton et al., 2004).

liver (MA:0000358)

Histopath Description:
diffuse lipidosis

Morphological Diagnosis:
Distribution: diffuse; **Severity:** extreme; **MPATH Diagnosis:** steatosis MPATH:622; **MPATH Process Term:** lipid deposition MPATH:42

Definitive Diagnosis:
hepatic steatosis

Organ/Tissue Analyzed:
Histopathology examination included the following organs and tissues: brain, trigeminal ganglion, eyes, salivary glands, trachea, lungs, heart, thymus, thyroid gland, parathyroid gland, exocrine and endocrine pancreas, oesophagus, stomach, small intestine, large intestine, liver, gall bladder, spleen, kidneys, adrenal gland, lymph nodes, spinal cord, bone marrow, sternum, femur and tibia with associated skeletal muscles, brown fat, pinna, skin, uterus, oviduct, and ovary, and mammary gland.

Report Summary and Recommendation:
Retinal dysplasia is observed in two mice. This retinal lesion is consistent with those reported as a background lesion in C57BL/6N lines (Mattapallil et al., 2012). We did not see evidence of the iris and lens contrary to the clinical phenotype annotations. It is likely that the ocular lesion described for this line may be of low penetrance.

Eosinophilic spheroid bodies were noted in the deep cerebellar nuclei in one mouse. Similar lesion was noted in some mice from line 65 (Esco1 KO mice) from previous submission. Interestingly, the gene Esco1 is alos related to chromosome function. Further the morphology and the specific location of these bodies is very similar to those described in autophagy-related 4b (Agtb4b) mutants (Read et al., 2011). In addition, mice deficient for Atg5 (autophagy-related 5) specifically in neural cells develop progressive deficits in motor function that are accompanied by the accumulation of cytoplasmic inclusion bodies in neurons (Hara et al., 2006). These types of bodies are occasionally seen in old mice so their appearance in young mice is often associated with premature senility or autophagy defects. We suspect they represent the latter stages of axonal spheroids and dystrophic axons and neurites, basically an accumulation of incompletely digested endosomal/lysosmal contents and thus the connection to autophagy defects.

Two mice had inflammatory lesion (one with dermatitis and another with sialoadenitis suggestive of cytomegalovirus infection). This lesions may have relevance to the clinical phenotype (increased susceptibility to bacterial infection). Ancillary tests are required to confirm diagnosis of MCMV infection. MCMV lesions are often found in the salivary glands, and virus can be isolated from salivary glands or saliva from a majority of wild mice. Infection in laboratory mice has declined significantly in recent years and is apparently rare or nonexistent in most colonies. A single case of naturally occurring MCMV

disseminated infection has been reported in an aged laboratory mouse. Differential diagnosis includes polyoma virus. Other viruses that infect salivary glands include reovirus 3, mouse thymic virus, and mammary tumor virus, but these viruses do not induce inclusions (Percy and Barthold, 2007).

There are no lesions predictive of homozygous preweaning mortality.

Line summary:
Brain, deep cerebellar nuclei: eosinophilic spheroids (1/4).
Salivary gland: lymphocytic sialoadenitis with karyomegaly and intranuclear inclusions (1/4)
Auricular dermatitis with hyperplasia (1/4)

References:

Dean H. Percy and Stephen W. Barthold. PATHOLOGY OF LABORATORY RODENTS AND RABBITS. THIRD EDITION. Blackwell publishing. Page 19-21 Read R et al. (2011). Histopathological and Neurological Features of Atg4b Knockout Mice. Veterinary Pathology. 48:486-494. Hara T et al. (2006). Suppression of Basal Autopahy in Neural Crest Cells Causes Neurodegenerative Disease in Mice. Nature 441:885-886 Mattapallil MJ, Wawrousek EF, Chan CC, Zhao H, Roychoudhury J, Ferguson TA, Caspi RR. (2012). The Rd8 mutation of the Crb1 gene is present in vendor lines of C57BL/6N mice and embryonic stem cells, and confounds ocular induced mutant phenotypes. Invest Ophthalmol Vis Sci. 53:2921-2927.