CMHD Pathology Report

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ReportID: Report Date: June 20, 2013
Pathologist: Dr. H. Adissu

CMHD LabID: N13-468

Relevant History:
prenatal lethality
preweaning lethality

AnimalID: M00169704 (Male)

Histopathology Findings:

brain (MA:0000168)

Histopath Description:
There is mild dilation of the lateral ventricles

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

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).

eye (MA:0000261)

Histopath Description:
Involving one eye, there are clusters of external nuclear structures within the internal plexiform layer.

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

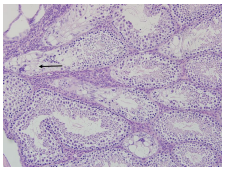
Definitive Diagnosis:
Retinal dysplasia

testis (MA:0000411)

Histopath Description:
Occasional seminieferous tubules are vacuolated and are devoid of germ cells or contain clusters of degenerate germ cells

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

Definitive Diagnosis:
Vacuolar degeneration and atrophy of the seminiferous tubule


Testis, vacuolar

degeneration and atrophy of the seminiferous tubule, 40x, HE

liver (MA:0000358)

Histopath Description:
moderate lipidosis

Morphological Diagnosis:
Distribution: multifocal to coalescing; **Severity:** moderate; **MPATH Diagnosis:** steatosis MPATH:622

Definitive Diagnosis:
Hepatic lipidosis

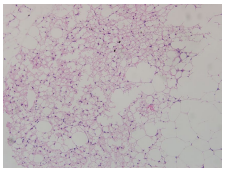
brown fat (MA:0000057)

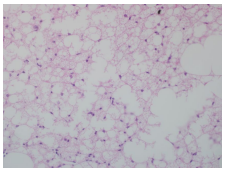
Histopath Description:
Representing less than 10% of the examined brown fat, there are areas focal to multifocal clusters of plump cells with basophilic cytoplasm and plump spindloid nucleus (interpreted as preadiposites) and small adipocytes with basophilic microvesiculated cytoplasm and central basophilic round nucleus (interpreted as young adipocytes). There are rare lymphocyte-like cells associated with these foci (it was not possible to determine with certainty if these represented degenerating adipocytes or inflammatory cells).

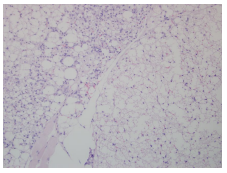
Morphological Diagnosis:
Distribution: multifocal; **Severity:** mild;

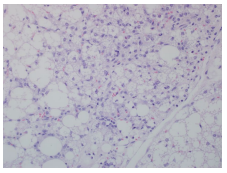
Definitive Diagnosis:
Multifocal adipogenesis and lipogenesis

Histopathology Comments:
See comment for M00169706


Brown fat, wildtype, normal, 20x, HE


Brown fat, wildtype, normal, 40x, HE


Brown fat, Multifocal adipogenesis and lipogenesis, 20x, HE


Brown fat, Multifocal adipogenesis and lipogenesis, 40x, 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: M00169703 (Male)

Histopathology Findings:

brain (MA:0000168)

Histopath Description:
There is mild dilation of the lateral ventricles

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

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:
Diffused lipidosis

Morphological Diagnosis:
Distribution: diffuse; **Severity:** severe; **MPATH Diagnosis:** steatosis MPATH:622

Definitive Diagnosis:
Hepatic lipidosis

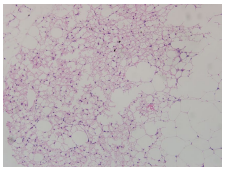
brown fat (MA:0000057)

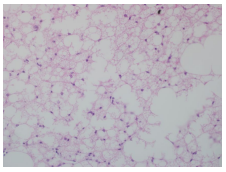
Histopath Description:
Representing less than 10% of the examined brown fat, there are areas focal to multifocal clusters of plump cells with basophilic cytoplasm and plump spindloid nucleus (interpreted as preadiposites) and small adipocytes with basophilic microvesiculated cytoplasm and central basophilic round nucleus (interpreted as young adipocytes). There are rare lymphocyte-like cells associated with these foci (it was not possible to determine with certainty if these represented degenerating adipocytes or inflammatory cells).

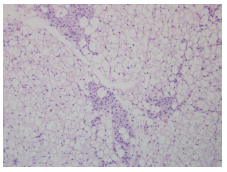
Morphological Diagnosis:
Distribution: multifocal; **Severity:** mild;

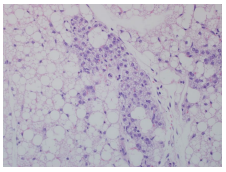
Definitive Diagnosis:
Multifocal adipogenesis and lipogenesis

Histopathology Comments:
See comment for M00169706


Brown fat, wildtype, normal, 20x, HE


Brown fat, wildtype, normal, 40x, HE


Brown fat, Multifocal adipogenesis and lipogenesis, 20x, HE


Brown fat, Multifocal adipogenesis and lipogenesis, 40x, 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: M00169706 (Female)

Histopathology Findings:

brain (MA:0000168)

Histopath Description:
There is mild dilation of the lateral ventricles

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

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).

lymph node (MA:0000139)

Histopath Description:
The mesenteric lymph node is enlarged (greater than three-fold). There are multiple follicles with large germinal centers. The sinuses contain large numbers of mature lymphocytes and plasma cells.

Morphological Diagnosis:
Duration: Sub-acute; **Distribution:** Diffuse; **Severity:** moderate; **MPATH Diagnosis:** hyperplasia MPATH:134

Definitive Diagnosis:
Lymphoid hyperplasia with sinus plasmacytosis

Histopathology Comments:
The changes in the mesenteric lymph node are suggestive of draining of a regional inflammatory process. However, such a process was not observed in the tissues examined.

stomach (MA:0000353)

Histopath Description:
moderate neutrophilic gastritis

Morphological Diagnosis:
Distribution: multifocal to coalescing; **Severity:** moderate;

Definitive Diagnosis:
Gastrits, neutrophilic

eye (MA:0000261)

Histopath Description:
Involving one eye, there are clusters of external nuclear structures within the internal plexiform layer.

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

Definitive Diagnosis:
Retinal dysplasia

liver (MA:0000358)

Histopath Description:
moderate lipidosis

Morphological Diagnosis:
Distribution: multifocal to coalescing; **Severity:** moderate; **MPATH Diagnosis:** steatosis MPATH:622

Definitive Diagnosis:
Hepatic lipidosis

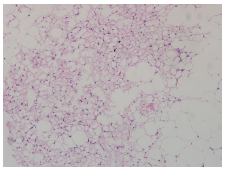
brown fat (MA:0000057)

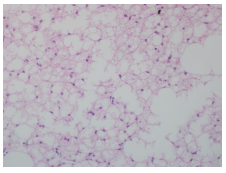
Histopath Description:
Representing less than 10% of the examined brown fat, there are areas focal to multifocal clusters of plump cells with basophilic cytoplasm and plump spindloid nucleus (interpreted as preadiposites) and small adipocytes with basophilic microvesiculated cytoplasm and central basophilic round nucleus (interpreted as young adipocytes). There are rare lymphocyte-like cells associated with these foci (it was not possible to determine with certainty if these represented degenerating adipocytes or inflammatory cells).

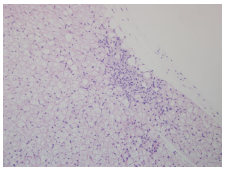
Morphological Diagnosis:
Distribution: multifocal; **Severity:** mild;

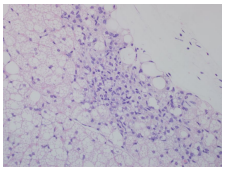
Definitive Diagnosis:
Multifocal adipogenesis and lipogenesis

Histopathology Comments:
These focal changes are occasionally seen in mice usually associated with mild inflammation (usually described as proliferative steatitis). The inflammatory component is very minimal in this case. We are not certain if the lesion represents a post inflammatory regereration or a primary impairement of lipogenesis or blocked adipogenesis (differentiation of preadipocytes to adipocytes). Note that all mice in this line have various degrees of this lesion in either the brown or white fat (see summary)


Brown fat, wildtype, normal, 20x, HE


Brown fat, wildtype, normal, 40x, HE


Brown fat, Multifocal adipogenesis and lipogenesis, 20x, HE


Brown fat, Multifocal adipogenesis and lipogenesis, 40x, 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: M00169666 (Female)

Histopathology Findings:

brain (MA:0000168)

Histopath Description:
There is mild dilation of the lateral ventricles

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

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).

eye (MA:0000261)

Histopath Description:
Involving one eye, there are clusters of external nuclear structures within the internal plexiform layer.

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

Definitive Diagnosis:
Retinal dysplasia

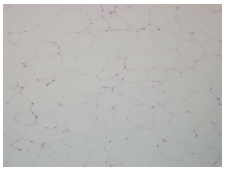
white fat (MA:0000058)

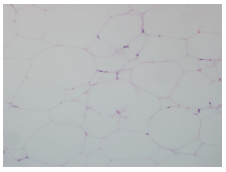
Histopath Description:
Within the white fat (adjacent to the submitted brown fat) there is a focally extensive clusters of plump cells with basophilic cytoplasm and plump spindloid nucleus (interpreted as preadiposites) and small adipocytes with basophilic microvesiculated cytoplasm and central basophilic round nucleus (interpreted as young adipocytes). There are rare lymphocytes associated with these foci.

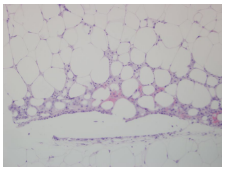
Morphological Diagnosis:
Distribution: multifocal; **Severity:** mild;

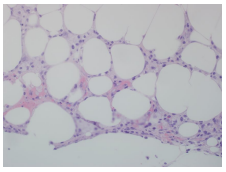
Definitive Diagnosis:
Multifocal adipogenesis and lipogenesis

Histopathology Comments:
See comment for M00169706


White fat, wildtype, normal, 20x, HE


White fat, wildtype, normal, 40x, HE


White fat, Multifocal adipogenesis and lipogenesis, 20x, HE


White fat, Multifocal adipogenesis and lipogenesis, 40x, HE

liver (MA:0000358)

Histopath Description:
moderate lipidosis

Morphological Diagnosis:
Distribution: multifocal to coalescing; **Severity:** moderate; **MPATH Diagnosis:** steatosis MPATH:622

Definitive Diagnosis:
Hepatic lipidosis

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:
Vacuolar degeneration and atrophy is noted in one of the male mice. AGPAT3 is highly expressed in the

testis and is considered an alternative important acyltransferase to produce phosphatidylinositol in the testis (Yuki et al., 2009).

Minimal focal to multifocal areas of adipogenesis of brown and white fat are noted in all mice in this line. These changes are minimal and are occasionally seen in wildtype and mutant mice usually associated with mild inflammation (diagnosed as proliferative steatitis in some mice from WTSI submissions). The inflammatory component is very minimal in the current case; hence we are not certain if it represents a post inflammatory regenerative hyperplasia or a primary impairment of lipogenesis or blocked adipogenesis (differentiation of preadipocytes to adipocytes).

The presence of this lesion in all mice in this line is interesting in light of the role of a related gene (Agpat2) in congenital generalized lipodystrophy (CGL), a heterogeneous group of rare diseases associated with partial or total loss of adipose tissue. Of these, autosomal recessive Berardinelli-Seip congenital lipodystrophy (BSCL) is characterized by the absence of metabolically active subcutaneous and visceral adipose tissues (Vogel et al., 2011). Metabolic abnormalities associated with lipodystrophy include insulin resistance, hypertriglyceridemia, hepatic steatosis, and diabetes. One form of BSCL has been linked to genetic mutations affecting the lipid biosynthetic AGPAT2, which is highly expressed in adipose tissue. Impaired lipogenesis (triglyceride synthesis and storage), blocked adipogenesis (differentiation of preadipocytes to adipocytes), or apoptosis/necrosis of adipocytes has been suggested as possible mechanisms (Vogel et al., 2011).

Interestingly, complete depletion of fat was noted in aged Agpat2-/- mice (Vogel et al., 2011). In contrast there is a normal amount of fat in Agpat3+/- mice in all areas examined (subcutaneous, perinephric, mesenteric, and synovial fat. In light of the minimal lesions and the presence of normal amount of fat deposit in this line, we speculate severe lipodystrophic lesions in the homozygotes (Agpat3-/-). Marked lipodystrophic lesions were noted in one week old Agpat2-/- pups. Further, similar to Agpat3-/- mice, Agpat2-deficient mice have high neonatal mortality with most mice dying during the first 2 weeks of life. Agpat2-/- mice that survived past weaning were generally smaller than littermate controls, and relatively few survived to 3 months of age, because of continued high mortality rates after weaning (Vogel et al., 2011). Another significant finding in aged lipodystrophic mice was massive pancreatic islet hypertrophy in the face of chronic hyperglycemia (Vogel et al., 2011). We did not see any abnormality in pancreatic islets. Analysis of Agpat3-/- neonates and preweaning pups likely reveal lipodystrophic lesions as described for Agpat2-/- pups (Vogel et al., 2011).

References:

Vogel P, et al. (2011). Pathology of congenital generalized lipodystrophy in Agpat2-/- mice. Vet Pathol. 48(3):642-54. Yuki K, Shindou H, Hishikawa D, Shimizu T.J Lipid Res. 2009; 50(5):860-9.