Latin Comparative Pathology Group

The Latin Subdivision of the CL Davis Foundation

Diagnostic Exercise

Case #: 58 Month: July Year: 2015

Answer Sheet

Morphologic Diagnoses:

1. Kidneys, bilateral: Cystadenocarcinoma (Figure 1)

2. Lungs, adrenal gland, subcutis, skeletal muscle (left thigh): Multifocal metastatic cystadenocarcinoma

3. Dermis: multiple fibromas (Figure 2)

Typical Gross And Microscopic Findings: Dermatofibrosis and Renal cystadenocarcinomas (Figures 1 and 2)

Histologic Description (Figures 3 and 4): The majority of the renal cortex and medulla are replaced or compressed by multifocal to coalescing, expansile, multilobular masses composed of tubules, cords, and irregular papillary projections of cuboidal to polygonal cells arranged along collagenous fibrovascular septa. Papillary projections often protrude into lumina of cystic spaces, accompanied by sloughed, variably necrotic neoplastic cells, free red blood cells, and hemosiderin-laden macrophages. Cells have distinct borders and moderate amount of eosinophilic, finely granular cytoplasm, often with variably-sized clear cytoplasmic vacuoles. Nuclei are round, frequently central, and have finely stippled chromatin with indistinct nucleoli. Anisocytosis and anisokaryosis are mild to moderate, with rare multinucleate cells and six mitotic figures in ten 400x fields. The surrounding renal parenchyma is compressed, with regional tubular loss, interstitial fibrosis, and scattered lymphoplasmacytic inflammation. Persisting tubules range from ectatic to lined by piled, disorganized epithelium, and glomeruli are often subjectively small, with Bowman's spaces distended with proteinaceous fluid.

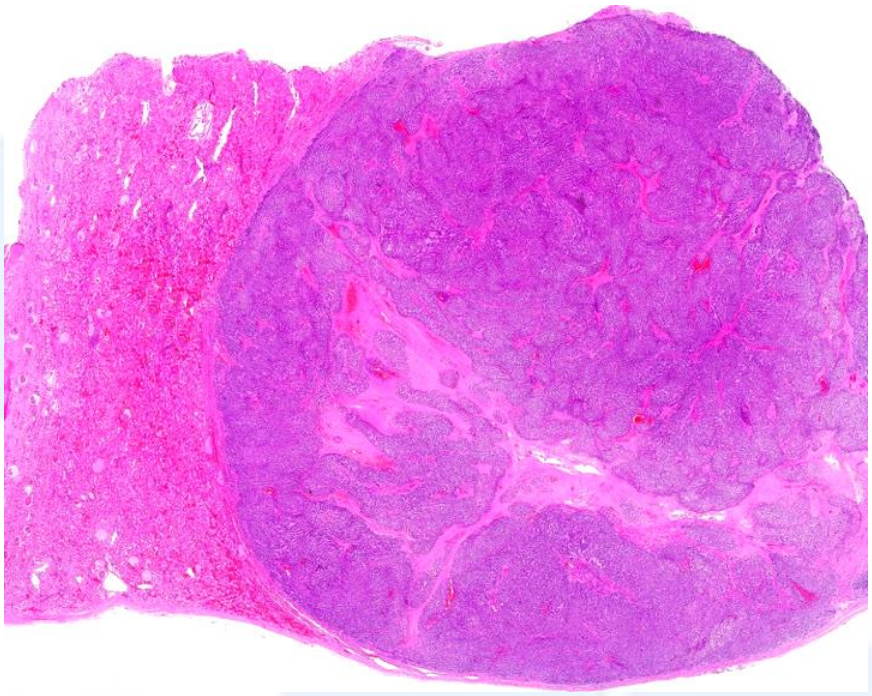

Figure 3

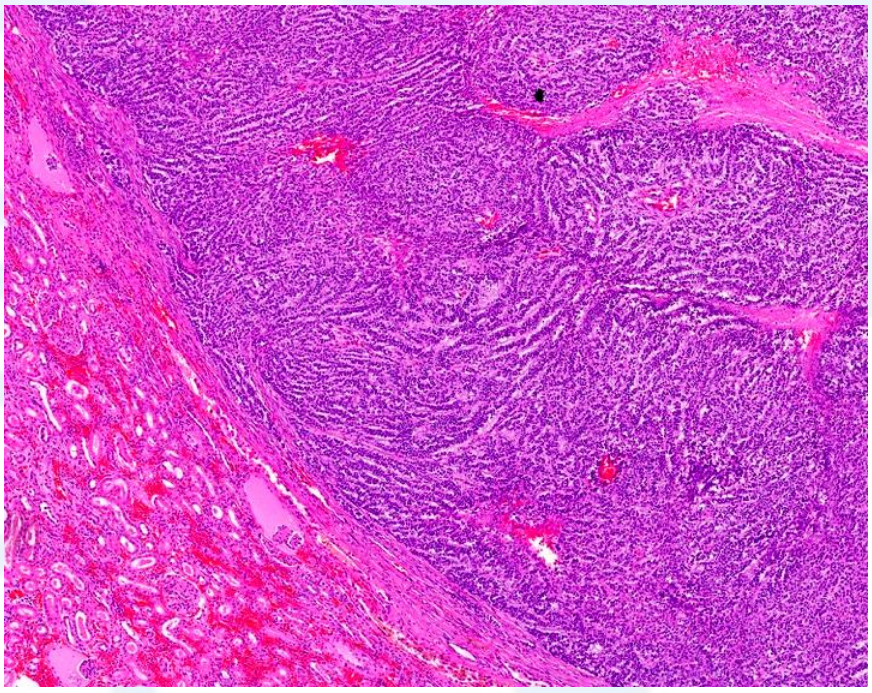

Figure 4

Additional Diagnostics (Molecular Genetics): Molecular genetic analysis was performed for a specific mutation of the FLCN gene (folliculin) and demonstrated heterozygosity for the mutation. A prior biopsy of a mass from the head (14B1733) was diagnosed as a collagenous hamartoma, compatible with nodular dermatofibrosis.

Discussion: In the presented case, the signalment, bilateral renal cystadenocarcinomas, confirmed folliculin mutation, and the collagenous dermal tumors fit the syndrome of hereditary multifocal renal cystadenocarcinoma and nodular dermatofibrosis (RCND) in German shepherd dogs.

RCND is a hereditary, autosomal dominant, canine renal cancer syndrome that was first characterized in German shepherd dogs (1). Typical lesions include bilateral, multifocal renal cystadenocarcinomas, multiple collagenous dermal nodules, and uterine leiomyomas in intact, mature females. Metastasis is reported in approximately 50% of cases (2). The RCND locus has been mapped to a region of canine chromosome 5, FLCN (previously BHD), which encodes the putative tumor suppressor protein folliculin (3,4,5,7). In dogs, RCND has been associated with a missense mutation in a conserved region of FLCN. The syndrome in dogs is similar to Birt-Hogg-Dubé syndrome in humans, which is caused by the same gene (on human chromosome 17), and is associated with renal tumors, pulmonary cysts, and cutaneous lesions that include fibrofolliculomas and acrochordons (6).

References and Recommended literature:

1. Lium B, Moe L. Hereditary multifocal renal cystadenocarcinomas and nodular dermatofibrosis in the German shepherd dog: macroscopic and histopathologic changes. Vet Pathol. 1985 Sep;22(5):447-55.
2. Moe L, Lium B. Hereditary multifocal renal cystadenocarcinomas and nodular dermatofibrosis in 51 German shepherd dogs. J Small Anim Pract. 1997 Nov;38(11):498-505.
3. Haas NB, Nathanson KL. Hereditary kidney cancer syndromes. Adv Chronic Kidney Dis. 2014 Jan;21(1):81-90.
4. Kuroda N, Furuya M, Nagashima Y, Gotohda H, Kawakami F, Moritani S, Ota S,Hora M, Michal M, Hes O, Nakatani Y. Review of renal tumors associated with Birt-Hogg-Dubé syndrome with focus on clinical and pathobiological aspects. Pol J Pathol. 2014 Jun;65(2):93-9.
5. Lingaas F, Comstock KE, Kirkness EF, Sørensen A, Aarskaug T, Hitte C, Nickerson ML, Moe L, Schmidt LS, Thomas R, Breen M, Galibert F, Zbar B, Ostrander EA. A mutation in the canine BHD gene is associated with hereditary multifocal renal cystadenocarcinoma and nodular dermatofibrosis in the German Shepherd dog. Hum Mol Genet. 2003 Dec 1;12(23):3043-53

6. Dal Sasso AA, Belém LC, Zanetti G, Souza CA, Escuissato DL, Irion KL, Guimarães MD, Marchiori E. Birt-Hogg-Dubé syndrome. State-of-the-art review with emphasis on pulmonary involvement. Respir Med. 2015 Mar;109(3):289-296.

7. Medvetz DA, Khabibullin D, Hariharan V, Ongusaha PP, Goncharova EA, Schlechter T, Darling TN, Hofmann I, Krymskaya VP, Liao JK, Huang H, Henske EP. Folliculin, the product of the Birt-Hogg-Dube tumor suppressor gene, interacts with the adherens junction protein p0071 to regulate cell-cell adhesion. PLoS One.2012;7(11):e47842.

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).