Hereditary Multifocal Renal Cystadenocarcinomas and Nodular Dermatofibrosis in the German Shepherd Dog: Macroscopic and Histopathologic Changes

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Abstract. A syndrome characterized by bilateral, multifocal renal cystadenocarcinomas and nodular dermatofibrosis was found in 43 German shepherd dogs. Affected kidneys varied in weight from normal to 2950 g. The cut surface revealed multiple solid and cystic tumors that varied in size from barely visible to 27 cm in diameter. Metastases were found in ten of the 23 dogs examined since 1979. All 23 dogs had numerous firm nodules in the skin and subcutis, and ten of 11 bitches had multiple uterine leiomyomas. Histological examination of the renal cortex showed multifocal hyperplastic to highly malignant epithelial proliferations. Skin lesions consisted of dense collagen fibers, and the uterine tumors consisted of interlacing bundles of smooth muscle cells. Pedigree analysis strongly indicates that the syndrome is hereditary, probably in an autosomal dominant pattern.

This seems to be the first description of such a syndrome in domestic animals. Comparable syndromes in man are discussed.

Materials and Methods

A retrospective study of the necropsy files of the Department of Pathology, the Norwegian College of Veterinary Medicine, from the years 1958 to 1978 revealed 22 German shepherd dogs with primary renal neoplasms. Post mortem records, available tissue samples and histological slides from these dogs were re-evaluated. During the years 1979 to 1983, a systematic gross and histomorphological examination of all primary renal neoplasms in German shepherd dogs (n = 23) was done. All dogs were killed by intravenous administration of a solution of 10% sodium pentobarbital, the majority were necropsied within a few minutes to one hour post mortem. Tissue sections were taken from the kidneys, skin, liver, lungs, and spleen and from other organs with gross pathological changes. From each dog, five to 15 tissue samples were taken, both from apparently normal and from grossly changed areas of each kidney, and five to ten samples were taken from various skin nodules. Tissue samples were fixed in 10% neutral-buffered formalin, embedded in paraffin, sectioned at 5 μm and stained with hematoxylin and eosin (HE) and van Gieson.

Forty-three of the 45 German shepherd dogs with primary renal tumors had a syndrome characterized by multifocal renal cystadenocarcinomas, numerous firm skin nodules, and in females, multiple uterine leiomyomas. Clinical records and breeding data of these dogs were studied regarding age, clinical symptoms, and pedigree. This paper describes the morphology of 23 affected German shepherd dogs necropsied since 1979.

Case Histories

The first dog with bilateral and multifocal renal cystadenocarcinomas combined with numerous firm skin nodules was necropsied in 1967. During the years 1967 to 1983, 43 of 1174 (3.7%) German shepherd dogs necropsied had this syndrome. In the same period, 45 of 57 (79%) primary renal neoplasms diagnosed in dogs were found in this breed. German shepherd dogs constituted 13% (1174 of 9068) of the total number of dogs necropsied.
At necropsy, the affected dogs, 24 females and 19 males, ranged from five to 11 years of age (average of 8.5 years). Clinical findings varied somewhat from case to case, but usually included numerous, very firm skin nodules, abdominal distention, and enlarged and abnormally shaped kidneys. Other clinical signs were loss of appetite, weakness and progressive loss of weight for weeks or months, polydipsia, vomiting, obstipation, diarrhea, and dermatitis. Recurrent gross hematuria was found in four of 19 dogs, and elevated blood urea was diagnosed in eight of 17 dogs examined. Case histories indicated that the disease had developed slowly over the years.

Breeding data were available from 37 of the 43 dogs necropsied, and from four affected dogs which were still alive. Pedigree analysis showed that the syndrome occurred in certain related families, and that all affected dogs could be traced back to a common male ancestor. In most cases, only one parent was related to this male.

Macroscopic examination

Kidneys: The kidneys were bilaterally enlarged and had a bumpy surface caused by protruding tense cysts and/or neoplastic tissue (figs. 1, 2). They varied in weight from normal (about 95 g) to 2950 g, and in size from normal to 27 × 17 × 10 cm. In the least changed case, both kidneys weighed 95 g, while the largest pair of kidneys weighed 2690 g and 1090 g, respectively. The renal lesions were most pronounced in the left kidney in 12 dogs and in the right kidney in eight dogs. The most enlarged kidneys were covered by a thickened fibrous capsule. In six dogs, this was adherent to the greater omentum, intestines and/or the uterus. In addition, ruptured cysts and mild peritonitis with an opaque, dark brown abdominal fluid were found in these six dogs.

On the cut surface, multiple cysts, ranging from barely visible to 27 cm in diameter, were found scattered in the renal cortex (fig. 3).

Each kidney had one to five large cysts (> 1 cm in diameter) and various numbers of smaller ones. The smallest cysts contained a clear, serous or coagulated fluid while larger cysts were filled with dark brown, opaque, pulpy fluid and/or blood coagulum. Some cysts contained a gray to brown muddy mass. No communication between the lumen of cysts and the renal pelvis could be detected. Large cysts were separated from the normal renal parenchyma by a thick fibrous capsule, and the inner lining was generally smooth and fibrous. In most, local proliferations of tumorous tissue were found projecting into the cyst lumen (figs. 3, 4). The neoplastic tissue was irregular, soft, friable, gray, and measured up to 5 cm in diameter.

Scattered solid neoplastic proliferations were also seen in the renal parenchyma, usually as gray foci of a few mm to about 4 cm in diameter. A few kidneys had solid neoplasms measuring up to 10 cm in diameter. This neoplastic tissue varied from soft and friable to very firm, and areas with hemorrhage and necrosis were seen. In advanced cases, the renal parenchyma was almost completely replaced by multiple cysts and solid tumors.

Metastases: Metastatic lesions were detected in ten dogs. Most formed small solid nodules or cysts (fig. 5). The sternal and renal lymph nodes were the most common sites for secondary growth. Metastases were also found in peritoneum, pleura, liver, lung, spleen, and bone. In one dog, the cranial sternal lymph node measured 10 cm in diameter and contained tense cysts filled with a grayish-brown fluid. In two others, the thoracic cavity was filled with 3 and 4½ l of serohemorrhagic fluid, respectively, and about 900 g of an orange-colored pulpy tumor mass, which was partially attached to the pleura and partially floating in the bloody fluid.

Skin: All dogs had firm, spherical to lenticular nodules in the skin and subcutis all over the body, but with marked predilection to the lower limbs, head and back (figs. 6, 7). The cut surface was white and fibrotic. At least 30 to 50 nodules were seen in each dog, and in advanced cases several hundred were found. Most nodules varied in size from a few mm to 1 cm in diameter, but some measured up to 4 cm in diameter, and in some dogs they had coalesced and formed irregular fibrotic masses. Skin nodules usually were covered by intact epidermis, but some of the largest nodules showed ulceration and secondary inflammation.

Uterus: Multiple uterine tumors were found in ten of 11 bitches (fig. 8). They varied in size from a few mm to 10 cm in diameter. The smaller tumors were seen as lenticular swellings of the uterine wall, while the larger tumors protruded from the serosal surface—some were pedunculated. Tumors were firm and gray to slightly yellow with no distinct delineation from the surrounding uterine tissue. Hemorrhage and necrosis were seen in the largest tumors.

Other lesions: Hemoperitoneum and/or peritonitis were found in six dogs, and were associated with rupture of renal cysts. A faint icteric discoloration in three dogs seemed to be secondary to hemoperitoneum and metastatic tumors in the liver. Only two dogs had uremic lesions. The rest of the lesions seen at necropsy were incidental findings with no obvious correlation to the syndrome described in this paper.

Microscopical examination

The histological features of the kidneys, skin, and uterine neoplasms were similar in all dogs.

Kidneys: Sections from areas of renal cortex, with only slight macroscopic changes, revealed multifocal hyperplastic to dysplastic proliferations and neoplastic transformations of renal tubular epithelial cells. In these epithelial proliferations, renal tubules formed small irregular dilatations with transition to cysts, covered with cuboidal to cylindrical epithelium and papillary projections into the cyst lumen (figs. 9, 10). Most epithelial cells in such proliferations closely resembled normal tubular cells, although many cells were enlarged with cosinophilic cytoplasm and enlarged nuclei with prominent nucleoli. Mitotic figures were rare, though there were some binucleated cells. Some cells had peculiar vacuoles and small cysts within their cytoplasm. The stroma was scanty with thin fibrovascular cords and there was no evident demarcation to normal parenchyma.

Though most of the inner surface of large cysts was necrotic or covered with cuboidal epithelium, local irregular papillary proliferations of epithelial cells, similar to those described above, were also seen (fig. 11). Hemorrhage and necrosis were frequently found, especially at the top of the papillary prolif-
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Fig. 1: Enlarged kidney with four large projecting cysts. Bar = 1 cm.

Fig. 2: Moderately enlarged kidney with projecting cysts at poles. Bar = 1 cm.

Fig. 3: Cut surface of kidney with multiple cysts and focal areas with solid neoplasms (arrows). Irregular neoplastic tissue on cyst wall (arrowheads).

Fig. 4: Neoplastic proliferation on inner surface of large cyst.

Erythrocytes and necrotic epithelial cells were found in the cyst lumen. Large cysts were surrounded by a macrophage-infiltrated thick fibrous capsule that blended into the surrounding atrophic renal tissue. In advanced cases, the remaining renal parenchyma had chronic degenerative changes with sclerotic glomeruli and interstitial fibrosis with scattered mononuclear cell infiltration.

Solid tumors consisted of pleomorphic, cuboidal to polygonal and sometimes highly undifferentiated cells with a slightly eosinophilic cytoplasm. The undifferentiated cells varied from sheets of small hyperchromatic spindle-shaped cells to large, anaplastic cells with monstrous nuclei and a very high frequency of bizarre mitotic figures (fig. 12). Solid tumors had a marked tendency to local infiltration, and hemorrhages and necroses were frequently seen.

Metastases: The histological pattern exhibited by the metastatic lesions found in ten dogs was similar to that seen in the primary renal tumors. Proliferating metastatic epithelial cells were sometimes found in the lumen of lymph and blood vessels, especially in the regional lymph nodes, liver, and lungs (figs. 13, 14).

Skin: Most of the skin and subcutaneous nodules consisted of irregular bundles of dense collagen fibers with few fibrocytes (fig. 15). There was no marked demarcation from the surrounding connective tissue. Secondary inflammation with infiltrates of polymorphonuclear leukocytes and plasma cells
Fig. 5: Metastatic lesions in liver and liver lymph node.
Fig. 6: Large skin nodules with alopecia, ulceration, and secondary inflammation.
Fig. 7: Multiple, firm, lenticular nodules in subcutis.
Fig. 8: Multiple uterine leiomyomas, one of which is twisted.

was seen in some of the largest nodules as well as some of the intracutaneous ones.

Uterus: The uterine tumors were composed of interlacing bundles of smooth muscle fibers with characteristic cigar-shaped nuclei (fig. 16). The fibers tended to intersect at right angles. Mitotic figures were rare, and degenerative changes were only seen in some of the large and pedunculating tumors. Amounts of collagen and fibroblastic cells varied from tumor to tumor, but were generally scant.

Discussion

Sporadic occurrence of different primary neoplasms in different organs in the same dog is relatively common in dogs, but as far as we know this is the first description of hereditary multifocal primary neoplasms of different types in the kidneys, skin, and uterus.

Multifocal renal cystadenocarcinomas as described in this report have been seen solely in German shepherd dogs and have features quite different from previously described renal tumors in domestic animals. All reports of primary renal neoplasms in dogs conclude that there is no family or breed predisposition to develop such tumors, and the incidence is much lower than in our dogs. In a survey of 10,418 necropsied dogs, a total of only 15 primary renal tumors, of which only
seven were renal cell carcinomas, were recorded. A histological survey of 2,500 German shepherd dogs revealed only two dogs with renal neoplasms. This is in contrast to our material, in which renal neoplasms were found in 45 of 1,174 German shepherd dogs; 43 of these neoplasms were multifocal and bilateral cystadenocarcinomas. Most authors state that there is no sex prevalence in the development of renal cell carcinomas in dogs, though male dogs are over-represented in some reports. Although there is a numerical over-representation of female dogs in our material, there is no significant sex prevalence. The age of affected dogs (mean 8.5 years) is in accordance with the age of dogs with sporadic primary renal tumors. The multifocal and bilateral localization of renal cell proliferations in all these dogs indicates that the tumors had a primary multicentric origin. This is in contrast to the sporadic form of renal carcinoma in which tumors are usually found to be unilateral and solitary, with occasional metastases to the opposite kidney. In a survey of the literature, it was found that bilateral involvement was recorded in only four dogs. Multiple, well-differentiated adenocarcinomas in situ in both kidneys of a dog have been described. In renal carcinoma in man,
only 15% of the patients have multifocal lesions and less than 1% have bilateral lesions.\(^2\)

The scattered epithelial cell proliferations in the renal cortex seem to be pre-neoplastic changes which develop progressively from hyperplasia to adenomas and adenocarcinomas. These epithelial proliferations are remarkably similar to the renal lesions seen after experimental administration of carcinogenic substances.\(^5,19,20\)

The relationship between proliferation of renal epithelial cells and the formation of cysts has not yet been clarified. There is morphological evidence to suggest that proliferating epithelial cells may cause local obstruction by mechanical blockage and subsequent cystic dilatation of proximal segments. The marked tendency to hemorrhage and necrosis in papillary proliferations is thought to explain the dark fluid and blood coagulum seen in many cysts. This may also explain the fact that only focal and relatively small amounts of neoplastic
tissue were found on the inner lining of large cysts. Electron microscopical and immunological studies have demonstrated that renal cell tumors in man arise from the proximal convoluted tubules.6,25,30,32 A similar origin is suggested for sporadic canine renal cell carcinomas.1,34 In our material, the least changed proliferating tubular structures resembled proximal tubules. Nevertheless, the exact origin of the neoplastic cells need to be elucidated by further investigation.

The hereditary renal tumors in German shepherd dogs seem to metastasize with the same or a slightly lower frequency than sporadic canine renal cell carcinomas. Metastases seemed to occur most frequently and to be most numerous in dogs with large, solid renal tumors with a poorly differentiated histological pattern. Metastases were most commonly located in the cranial sternal lymph node, paraaortic lymph nodes, liver and lungs. This corresponds well with the locations of metastatic lesions in sporadic renal carcinomas, which frequently metastasize via the blood and lymphatic channels.1,13,22

The morphology of the cutaneous and subcutaneous nodules seen in all our dogs seems to be identical with a condition recently described as "generalized nodular dermatofibrosis." The first pathological description of this condition in dogs was reported in a brief communication.31 According to these authors, comparable skin lesions occur in man, namely generalized congenital fibromatosis, shagreen patches, dermatofibrosis lenticularis of the Buschke-Ollendorff syndrome and disseminated connective tissue nevi. They also noted that two of the six German shepherd dogs had renal cystadenocarcinomas, and we suggest that the lesions found in their dogs may have been identical with the syndrome described in this report. Apparently identical skin lesions were recently described as multiple, collagenous nevi on the distal limbs and head of five German shepherd dogs.29 The report was based on biopsy material of the skin without including kidney changes, and in our opinion these dogs might have suffered from the syndrome discussed in this paper.

The multiple uterine leiomyomas in ten of the 11 female dogs seem to be a part of the same syndrome. Similar uterine tumors were only sporadically seen in other dogs necropsied at our department between 1979 and 1983. The amount of collagen and fibroblastic cells varied somewhat from tumor to tumor, but was generally scanty. Leiomyomas are rare, while fibroleiomyomas are by far the most frequent genital tract tumor in dogs; it is usually multicentric.22

There are pathological entities in human medicine which are analogous, though not, in our opinion, identical to the syndrome in German shepherd dogs. Multiple, bilateral renal cysts and renal tumors, both adenomas and carcinomas, are frequently observed in human patients suffering from von Hippel-Lindau disease, a rare autosomal dominant disorder.9,12,15,26 In addition to renal cysts and neoplasms, this syndrome is characterized by retinal angiomatosis, cerebellar cysts, cerebellar, medullary and spinal angioblastomas, pancreatic cysts and pheochromocytomas. Such extrarenal pathological changes have not been observed in our dogs. It is, however, worth noting that the manifestation of the human syndrome varies greatly from case to case.

Neurofibromatosis (von Recklinghausen's disease) and tuberous sclerosis (Bourneville's disease) are other comparable syndromes in man with a high incidence of numerous cutaneous neoplastic nodules and multiple renal neoplasms.3,8,23,26,27 Both these syndromes are inherited in an autosomal dominant pattern. In contrast to our findings, the renal neoplasms seen in tuberous sclerosis are usually designated as hamartomas or angiomyolipomas.8,27 Skin lesions have not been described in the recently reported hereditary, multifocal renal carcinoma in man.2,4

The underlying causes of renal carcinoma have not been clarified. Environmental factors have been suggested as being of importance, and hormones may play a modulating role.11,14,32 The role of environmental factors is supported by experimental studies with administration of exogenous carcinogenic substances.5,19,20 It seems, however, most improbable that the renal tumors found in these German shepherd dogs, all living under different conditions, could have been caused by a common exogenous carcinogenic factor.

In man, it is well known that many types of cancer tend to occur in certain families, and a hereditary mechanism has been postulated on the basis of pedigree analysis.7,20 In most cases, however, the hereditary nature of the condition has not been satisfactorily established. Recently an author described a family in which a predisposition to develop multifocal bilateral renal carcinomas was transmitted in an autosomal dominant pattern; the disease was associated with a translocation between chromosome 3 and 8.4

Although pedigree analysis of affected German shepherd dogs strongly indicates that the disease is inherited, probably in an autosomal dominant pattern, the basic etiological and pathogenetic mechanisms of the renal and cutaneous lesions described in this report are still
unknown. Preliminary studies have not revealed any chromosomal abnormalities in our German shepherd dogs.

This seems to be the first detailed pathological description of a hereditary syndrome in domestic animals characterized by multifocal and bilateral renal cystadenocarcinomas, numerous collagen-rich skin nodules and uterine leiomyomas. Further studies are required to elucidate the basic pathogenetic mechanisms, the mode of heredity and the relationship to comparable syndromes in man. We believe that this disease in German shepherd dogs may be a valuable model for the study of basic mechanisms that lead to the development of renal carcinomas in man and animals.

References

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